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AF
JFW

JENKINS
WILSON
&TAYLOR

patent attorneys

RICHARD E. JENKINS

JEFFREY L. WILSON

ARLES A. TAYLOR, JR.

GREGORY A. HUNT

E. ERIC MILLS

BENTLEY J. OLIVE

*CHRIS PERKINS, PH.D.

**JAMES DALY IV, PH.D.

JEFFREY CHILDERS, PH.D.

P. ASHLEY DARDEN

CHRISTOPHER B. LEE

TECHNICAL SPECIALIST
AMY ODENBAUGH, PH.D.

*LICENSED ONLY IN CA

**LICENSED ONLY IN KY

December 20, 2005

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Date of Deposit December 20, 2005
I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Amy Yost
Amy Yost

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: U.S. Patent Application Serial No. 08/808,827 for
NON SELF-INACTIVATING, EXPRESSION TARGETED
RETROVIRAL VECTORS
Our Ref. No. 1406/194

Sir:

Please find enclosed the following:

1. An Appeal Brief (113 pages);

2. Response to Non-Compliant Appeal Brief (2-pages);

3. Statement Related to Entry of Declaration into the Record (1 page);

4. A return-receipt postcard to be returned to our offices with the U.S. Patent and Trademark date stamp thereon; and

5. A Certificate of Express Mail No.: EV733194918US.

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON & TAYLOR, P.A.

Arles A. Taylor, Jr.
Registration No.: 39,395
Customer No. 25297

AAT/CPP/acy

Enclosures

PATENT
(After Final)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gunzburg and Saller

Group Art Unit: 1631

Serial No.: 08/808,827

Examiner: Brusca, John S.

Filed: February 28, 1997

Docket No.: 1406/194

Confirmation No.: 6837

For: NON SELF-INACTIVATING, EXPRESSION TARGETED RETROVIRAL VECTORS

* *

RESPONSE TO NOTIFICATION OF NON-COMPLIANT APPEAL BRIEF (37 C.F.R. 41.37)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This paper is being submitted in response to a Notice of Non-Compliant Appeal Brief (37 C.F.R. 4137) dated December 9, 2005. Favorable reconsideration is respectfully requested in view of the enclosed Appeal Brief under 37 C.F.R. 41.37 and Remarks.

REMARKS

A Notice of Non-Compliant Appeal Brief (37 C.F.R. 41.37; hereinafter the "Notice") was issued on December 9, 2005. The Notice indicates that the Appeal Brief did not contain certain items required under 37 C.F.R. 41.37(c). The Notice further indicates that the missing item is a copy of a Rule 132 Declaration of Christine Leib-Moesch relied upon in the appeal.

Submitted herewith is an updated Appeal Brief. The updated Appeal Brief is identical to the Appeal Brief as originally submitted with the exception of the updating of Section IX, the Evidence Appendix, to include a true and accurate copy of the Rule 132 Declaration and a statement related to entry of the Declaration into the record. The statement appears on page 106, and the true and accurate copy of the Rule 132 Declaration now appears on pages 107-112.

Additionally, page 107 (now page 113) has been updated, with the paragraph originally appearing as subsection X.1 now appearing in subsection IX.1. Section X, the Related Proceedings Appendix, has been updated to indicate that there are no current Related Proceedings.

DEPOSIT ACCOUNT

Although it is believed that no fee is due for the filing of this correspondence, the Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: 20 Dec. 2005 By: _____

Arles A. Taylor, Jr.
Registration No. 39,395

1406/194 AAT/CPP/acy
Customer No: 25297

"Express Mail" mailing number: EV733194918US
Date of Deposit December 20, 2005
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Amy Yost

PATENT
(After Final)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gunzburg and Saller Group Art Unit: 1631

Serial No.: 08/808,827 Examiner: Brusca, John S.

Filed: February 28, 1997 Docket No.: 1406/194

Confirmation No.: 6837

For: NON SELF-INACTIVATING, EXPRESSION TARGETED RETROVIRAL VECTORS

* *

STATEMENT RELATED TO ENTRY OF DECLARATION INTO THE RECORD

The Rule 132 Declaration of Christine Leib-Moesch, a true and accurate copy of which is submitted herewith, was originally submitted to the United States Patent and Trademark Office on April 18, 2005. In an Advisory Action dated May 26, 2005, Examiner John S. Brusca indicated that the Declaration had been entered into the record.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: 20 Dec. 2005 By:

Arles A. Taylor, Jr.
Registration No. 39,395

1406/194 AAT/CPP/acy

Customer No: 25297

"Express Mail" mailing number: EV733194918US
Date of Deposit: December 20, 2005
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Amy Yost

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant	:	Gunzburg and Saller	)	
			)	Group Art Unit: 1631
Appln. No.	:	08/808,827	)	
			)	Examiner: John S. Brusca
Filed	:	February 28, 1997	)	

For: : NON SELF-INACTIVATING, EXPRESSION TARGETED RETROVIRAL VECTORS

* * * * * * * * * * *

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal pursuant to 35 U.S.C. § 134 from the Examiner's decision rejecting claims 1, 5, 7, 9-26, 28, 29, and 31-78 as set forth in the Final Official Action dated October 26, 2004.

I. Real Party in Interest

The real party in interest is GSF-Forschungszentrum für Umwelt und Gesundheit GmbH (hereinafter "GSF"), a corporation duly organized under the laws of the country of Germany, and the assignee of the inventors' entire interest by virtue of an

Assignment from the Bavarian Nordic Research Institute A/S, an original co-assignee along with GSF.

II. Related Appeals and Interferences

There are no appeals or interferences, known to appellant or appellant's legal representatives, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status of Claims

Claims 1, 5, 7, 9-26, 28, 29, and 31-78 are pending in the subject application. Claims 2-4, 6, 8, 27, 30, and 79-101 have been canceled by appellant. Claims 1, 5, 7, 9-26, 28, 29, and 31-78 stand finally rejected as per the Final Official Action of October 26, 2004, and are the subject of this Appeal.

IV. Status of Amendments

An Amendment after Final Rejection and a Request for Continued Examination were filed on September 2, 2004. The Final Official Action dated October 26, 2004 (hereinafter the "Final Official Action") indicated that the amendment was entered.

Additionally, a Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Christine Leib-Moesch was submitted on April 18, 2005. In a communication dated May 26, 2005, Examiner John S. Brusca indicated that the Declaration was entered into the record.

V. Summary of Claimed Subject Matter

This summary is presented in compliance with the requirements of 37 C.F.R. § 41.37(c)(1)(v), mandating a "concise explanation of the subject matter defined in each of the independent claims involved in the appeal". Nothing stated within this summary is to be interpreted as changing the specific language of the claims, nor is the language of this summary intended to be construed so as to limit the scope of the claims in any way.

Independent claim 1 recites a retroviral vector that undergoes promoter conversion. The retroviral vector comprises in 5' to 3' order:

(a) a 5' long terminal repeat region of the structure U3-R-U5 (Figures 3, 6, 10, and 11; page 6, lines 3-6);

(b) one or more coding sequences, said sequences being inserted into the body of the vector (Figures 3, 6, 10, and 11; page 6, lines 6-7); and

(c) a 3' long terminal repeat region comprising a partially deleted U3 region (Figure 11; page 6, lines 7-10) into which a polylinker sequence containing a heterologous promoter has been inserted (Figure 3; page 6, lines 19-28),

wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous promoter and said heterologous promoter regulating expression of said one or more coding sequences in said target cell (Figure 11; page 9, line 29, to page 10, line 3).

To summarize, independent claim 1 recites a non-self-inactivating retroviral vector that comprises in 5' to 3' order (a) a 5' LTR; (b) a coding sequence inserted into the body of the vector; and (c) a recombinant 3' LTR, wherein part of the U3 region of the 3' LTR has been deleted, and into the region of the deletion has been cloned a polylinker, into which has been inserted a heterologous promoter. Upon infection of a target cell by a retroviral particle encoded by the retroviral vector, the heterologous promoter becomes operatively linked to the coding sequence present in the body of the vector as a result of the reverse transcription event. In those cell types where the heterologous promoter is active, the coding sequence will be expressed.

Independent claim 17 recites a retroviral vector kit comprising

(a) a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

(i) a 5' long terminal repeat region of the structure U3-R-U5 (Figures 3, 6, 10, and 11; page 6, lines 3-6);

(ii) one or more coding sequences, said sequences being inserted into the body of the vector (Figures 3, 6, 10, and 11; page 6, lines 6-7); and

(iii) a 3' long terminal repeat region comprising a partially deleted U3 region (Figure 11; page 6, lines 7-10) into which a polylinker sequence containing a heterologous promoter has been inserted (Figure 3; page 6, lines 19-28) wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous promoter,

resulting in said one or more coding sequences becoming operatively linked to said heterologous promoter and said heterologous promoter regulating expression of said one or more coding sequences in said target cell (Figure 11; page 9, line 29, to page 10, line 3) and

(b) a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged (Figure 1; page 12, line 33, through page 13, line 15).

Thus, independent claim 17 essentially recites a retroviral vector kit comprising the retroviral vector of claim 1 and a packaging cell line appropriate for packaging the retroviral vector of claim 1 into retroviral particles.

Independent claim 28 recites a producer cell line producing a retroviral particle, the producer cell comprising a retroviral vector and a DNA construct coding for proteins required for the retroviral vector to be packaged (Figure 1; page 12, line 33, through page 13, line 15), said retroviral vector comprising in 5' to 3' order,

(a) a 5' long terminal repeat region of the structure U3-R-U5 (Figures 3, 6, 10, and 11; page 6, lines 3-6);

(b) one or more coding sequences, said sequences being inserted into the body of the vector (Figures 3, 6, 10, and 11; page 6, lines 6-7); and

(c) a 3' long terminal repeat region comprising a partially deleted U3 region (Figure 11; page 6, lines 7-10) into which a polylinker sequence containing a heterologous promoter has been inserted (Figure 3; page 6, lines 19-28),

wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous promoter and said heterologous promoter regulating expression of said one or more coding sequences in said target cell (Figure 11; page 9, line 29, to page 10, line 3).

To summarize, independent claim 28 essentially recites a producer cell line comprising a retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector of claim 1 to be packaged.

Independent claim 33 recites a retroviral vector which undergoes promoter conversion. The retroviral vector comprises in 5' to 3' order,

(a) a 5' long terminal repeat region of the structure U3-R-U5 (Figures 3, 6, 10, and 11; page 6, lines 3-6);

(b) one or more coding sequences, said sequences being inserted into the body of the vector (Figures 3, 6, 10, and 11; page 6, lines 6-7); and

(c) a 3' long terminal repeat region comprising a partially deleted U3 region (Figure 11; page 6, lines 7-10) into which a polylinker sequence containing a promoter from a cellular gene has been inserted (Figure 11; page 11, line 26, through page 12, line 6),

wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said promoter from a cellular gene, resulting in said one or more coding sequences becoming operatively linked to said promoter from a cellular gene and said promoter from a cellular gene regulating

expression of said one or more coding sequences in said target cell (Figure 11; page 9, line 29, to page 10, line 3).

To summarize, independent claim 33 essentially recites a retroviral vector as claimed in claim 1, wherein the heterologous promoter is a cellular promoter.

Independent claim 43 recites a retroviral vector kit comprising:

(a) a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

(i) a 5' long terminal repeat region of the structure U3-R-U5 (Figures 3, 6, 10, and 11; page 6, lines 3-6);

(ii) one or more coding sequences, said sequences being inserted into the body of the vector (Figures 3, 6, 10, and 11; page 6, lines 6-7); and

(iii) a 3' long terminal repeat region comprising a partially deleted U3 region (Figure 11; page 6, lines 7-10) into which a polylinker sequence containing a promoter from a cellular gene has been inserted (Figure 11; page 11, line 26, through page 12, line 6), wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said promoter from a cellular gene, resulting in said one or more coding sequences becoming operatively linked to said promoter from a cellular gene and said promoter from a cellular gene regulating expression of said one or more coding sequences

in said target cell (Figure 11; page 9, line 29, to page 10, line 3); and

(b) a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged (Figure 1; page 12, line 33, through page 13, line 15).

To summarize, independent claim 43 essentially recites a retroviral vector kit comprising the retroviral vector of claim 33 and a packaging cell line appropriate for packaging the retroviral vector of claim 33 into retroviral particles.

Independent claim 51 recites a producer cell line producing a retroviral particle, the producer cell comprising a retroviral vector and a DNA construct coding for proteins required for the retroviral vector to be packaged (Figure 1; page 12, line 33, through page 13, line 15), said retroviral vector comprising in 5' to 3' order,

(a) a 5' long terminal repeat region of the structure U3-R-U5 (Figures 3, 6, 10, and 11; page 6, lines 3-6);

(b) one or more coding sequences, said sequences being inserted into the body of the vector (Figures 3, 6, 10, and 11; page 6, lines 6-7); and

(c) a 3' long terminal repeat region comprising a partially deleted U3 region (Figure 11; page 6, lines 7-10) into which a polylinker sequence containing a promoter from a cellular gene has been inserted (Figure 11; page 11, line 26, through page 12, line 6),

wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said promoter from a cellular gene, resulting in said one or more coding sequences becoming operatively linked to

said promoter from a cellular gene and said promoter from a cellular gene regulating expression of said one or more coding sequences in said target cell (Figure 11; page 9, line 29, to page 10, line 3).

To summarize, independent claim 51 essentially recites a producer cell line comprising a retroviral vector of claim 33 and a DNA construct coding for proteins required for the retroviral vector of claim 33 to be packaged.

Independent claim 56 recites a retroviral vector which undergoes promoter conversion. The retroviral vector comprises in 5' to 3' order,

(a) a 5' long terminal repeat region of the structure U3-R-U5 (Figures 3, 6, 10, and 11; page 6, lines 3-6);

(b) one or more coding sequences, said sequences being inserted into the body of the vector (Figures 3, 6, 10, and 11; page 6, lines 6-7); and

(c) a 3' long terminal repeat region comprising a partially deleted U3 region (Figure 11; page 6, lines 7-10) into which a polylinker sequence containing a heterologous retroviral promoter has been inserted (Figure 11; page 11, line 26, through page 12, line 6),

wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous retroviral promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous retroviral promoter and said heterologous retroviral promoter regulating expression of said one or more coding sequences in said target cell (Figure 11; page 9, line 29, to page 10, line 3).

To summarize, independent claim 56 essentially recites a retroviral vector as claimed in claim 1, wherein the heterologous promoter is a heterologous retroviral promoter.

Independent claim 66 recites a retroviral vector kit comprising:

(a) a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

(i) a 5' long terminal repeat region of the structure U3-R-U5 (Figures 3, 6, 10, and 11; page 6, lines 3-6);

(ii) one or more coding sequences, said sequences being inserted into the body of the vector (Figures 3, 6, 10, and 11; page 6, lines 6-7); and

(iii) a 3' long terminal repeat region comprising a partially deleted U3 region (Figure 11; page 6, lines 7-10) into which a polylinker sequence containing a heterologous retroviral promoter has been inserted (Figure 11; page 11, line 26, through page 12, line 6), wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous retroviral promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous retroviral promoter and said heterologous retroviral promoter regulating expression of said one or more coding sequences in said target cell (Figure 11; page 9, line 29, to page 10, line 3); and

(b) a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged (Figure 1; page 12, line 33, through page 13, line 15).

To summarize, independent claim 66 essentially recites a retroviral vector kit comprising the retroviral vector of claim 56 and a packaging cell line appropriate for packaging the retroviral vector of claim 56 into retroviral particles.

Independent claim 74 recites a producer cell line producing a retroviral particle, the producer cell comprising a retroviral vector and a DNA construct coding for proteins required for the retroviral vector to be packaged (Figure 1; page 12, line 33, through page 13, line 15), said retroviral vector comprising in 5' to 3' order,

(a) a 5' long terminal repeat region of the structure U3-R-U5 (Figures 3, 6, 10, and 11; page 6, lines 3-6);

(b) one or more coding sequences, said sequences being inserted into the body of the vector (Figures 3, 6, 10, and 11; page 6, lines 6-7); and

(c) a 3' long terminal repeat region comprising a partially deleted U3 region (Figure 11; page 6, lines 7-10) into which a polylinker sequence containing a heterologous retroviral promoter has been inserted (Figure 11; page 11, line 26, through page 12, line 6),

wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous retroviral promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous retroviral promoter and said heterologous retroviral promoter

regulating expression of said one or more coding sequences in said target cell (Figure 11; page 9, line 29, to page 10, line 3).

To summarize, independent claim 74 essentially recites a producer cell line comprising a retroviral vector of claim 56 and a DNA construct coding for proteins required for the retroviral vector of claim 56 to be packaged.

Thus, independent claims 1, 33, and 56 recite retroviral vectors that undergo promoter conversion, wherein the vectors comprise a partial 3' U3 deletion into which is inserted a polylinker and a heterologous promoter, a cellular promoter, or a heterologous retroviral promoter, respectively. Independent claims 17, 43, and 66 recite kits comprising a packaging cells line and the retroviral vectors of claims 1, 33, and 56, respectively, and independent claims 28, 51, and 74 recite producer cell lines comprising the retroviral vectors of claim 1, 33, and 56, respectively.

VI. Grounds of Rejection to be Reviewed on Appeal

The grounds of rejection for review are as follows:

(A) The rejection of claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 under 35 U.S.C. § 103(a) as being unpatentable over Couture *et al.*, 1994 (5 *Human Gene Therapy* 667-677; hereinafter "Couture") in view of Faustinella *et al.*, 1994 (5 *Human Gene Therapy* 307-312; hereinafter "Faustinella");

(B) The rejection of claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78 under 35 U.S.C. § 103(a) as being unpatentable

over Couture in view of Faustinella, and further in view of Mee & Brown, 1990 (88 *Gene* 289-292; hereinafter "Mee");

(C) The rejection of claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-36, 38, 39, 42-49, and 51-55 under 35 U.S.C. § 103(a) as being unpatentable over Couture in view of Faustinella, and further in view of Mehigh *et al.*, 1993 (71 *J Anim Sci* 687-693; hereinafter "Mehigh");

(D) The rejection of claims 1, 13, 14, 33, 40, 41, 56, 63, and 64 under 35 U.S.C. § 103(a) as being unpatentable over any of:

(1) Couture in view of Faustinella as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 in (A) above;

(2) Couture in view of Faustinella as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 in (A) above, and further in view of Mee as applied to claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78 in (B) above; and

(3) Couture in view of Faustinella as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 in (A) above, and further in view of Mehigh as applied to claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-36, 38, 39, 42-49, and 51-55 in (C) above,

where each of the above three are as evidenced by Miller *et al.*, 1989 (7 *Biotechniques* 980-990; hereinafter "Miller") and Panganiban & Temin, 1984 (81 *PNAS* 7885-7889; hereinafter "Panganiban");

(E) The rejection of claims 1, 10, 33, 37, 56, and 60 under 35 U.S.C. § 103(a) as being unpatentable over any of:

(1) Couture in view of Faustinella as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 in (A) above;

(2) Couture in view of Faustinella as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 in (A) above, and further in view of Mee as applied to claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78 in (B) above; and

(3) Couture in view of Faustinella as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 in (A) above, and further in view of Mehigh as applied to claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-36, 38, 39, 42-49, and 51-55 in (C) above,

where each of the above three are further in view of Price *et al.*, 1987 (84 *PNAS* 156-160; hereinafter "Price"); and

(F) The rejection of claims 17, 20, 21, 26, 28, 43, 50-53, 66, and 73-76 under 35 U.S.C. § 103(a) as being unpatentable over any of:

(1) Couture in view of Faustinella as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 in (A) above;

(2) Couture in view of Faustinella as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 in (A)

above, and further in view of Mee as applied to claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78 in (B) above; and

(3) Couture in view of Faustinella as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 in (A) above, and further in view of Mehigh as applied to claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-36, 38, 39, 42-49, and 51-55 in (C) above,

where each of the above three are further in view of Longmore *et al.*, 1993 (82 *Blood* 2386-2395; hereinafter "Longmore"); and Kay *et al.*, 1993 (262 *Science* 117-119; hereinafter "Kay").

VII. Arguments

A. Rejection of claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 under 35 U.S.C. § 103(a) as being unpatentable over Couture in view of Faustinella

A.1. Argument for independent claim 1

The rejection of claim 1 as unpatentable over Couture in view of Faustinella should be reversed because the cited combination does not teach or suggest each and every element of the claim. Furthermore, there is no motivation to combine the references as suggested by the United States Patent and Trademark Office (hereinafter "the Patent Office") because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently

claimed subject matter. As such, appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 1.

A.1.a. The cited combination does not teach or suggest a partial 3' U3 deletion

The Patent Office asserts in the Final Official Action dated October 26, 2004, that Couture teaches retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses. The Patent Office further asserts that Faustinella shows in Figure 1 vector pS3, into which has been inserted a polylinker with unique cloning sites. The Patent Office contends that it would have been obvious to a person of ordinary skill in the art to modify the vectors of Couture by adding the multiple cloning site of Faustinella upon the contention that Faustinella shows that multiple cloning sites may be used to insert sequences of choice in a U3 region of a retroviral vector (*see* Final Official Action October 26, 2004, at page 4). Appellant respectfully traverse this contention.

Appellant respectfully submits that even assuming *arguendo* that Faustinella discloses a polylinker, the cited references cannot be combined as suggested by the Patent Office to arrive at the subject matter of claim 1 because adding a polylinker to Couture's vector does not create a retroviral vector with a partially deleted U3 region as recited in claim 1. Specifically, appellant respectfully submits that Couture in view of Faustinella do not teach a retroviral vector comprising a partially deleted U3 region as recited in claim 1.

In support of the instant rejection, the Patent Office asserts in the Final Official Action dated October 26, 2004, that Couture "shows a chimeric U3 region that was created by first deleting a portion of the original U3 region of the MuMLV based vector

and substituting portions of U3 regions from [five] different murine leukemia viruses" (Final Official Action dated October 26, 2004, at page 9). Appellant respectfully submits that this assertion is misleading, as Couture did not simply substitute portions of the U3 regions from these viruses, but rather replaced the sequences with the exactly corresponding sequences from five highly related murine retroviruses. This was accomplished using conserved restrictions sites present within the retroviral genomes, such that when the "portions" were cloned into the deletion, a complete 3' LTR was produced.

To elaborate, Couture explicitly states on page 669 that they built chimeric LTRs "based on the substitution of the MoMLV U3 region with the U3 region from the murine retroviral isolates SL3-3, AKV, Xeno, HaMSV, and MPSV" (emphasis added). This was accomplished by employing conserved restriction sites present in the 3' LTRs of these retroviruses. As such, the vectors disclosed by Couture were specifically designed to have complete U3 regions. This point is conceded by the Patent Office on page 3 of the Final Official Action dated October 26, 2004, where it is stated "Couture et al. shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses" (emphasis added). Therefore, appellant respectfully submits that Couture did not employ "portions" of the original U3 region (*i.e.*, subsets of the deleted sequences), but used conserved restriction sites to swap precisely corresponding sequences from the various U3 regions.

Thus, appellant respectfully submits that Couture does not disclose a retroviral vector with a partial 3' U3 deletion, and as such, even if a polylinker were added to the Couture vector, would not disclose or suggest the retroviral vectors of claim 1. The

assertion that Couture does not disclose vectors with partial 3' U3 deletions is supported by an Expert Declaration by Dr. Christine Leib-Moesch (hereinafter the "Leib-Moesch Declaration") submitted April 18, 2005, which states *inter alia*:

> [t]here is no disclosure in Couture of any retroviral vector in which the U3 region of the 3' LTR contains a deletion. Rather, Couture teaches producing complete, although chimeric, 3' LTRs by "swapping" corresponding regions of the 3' U3 sequences of five related retroviruses into the vector.

Leib-Moesch Declaration at page 2.

Thus, appellant respectfully submits that it cannot be said that the finally constructed retroviral vectors of Couture have a deletion of the U3 region. The vectors themselves (*i.e.*, the vectors that Couture considered useful) intentionally inserted the exactly corresponding 3' U3 sequences from a related retrovirus.

The retroviral vectors of claim 1, in contrast to the teachings of the cited combination, are characterized by incomplete 3' LTRs. Claim 1 recites, *inter alia*, a retroviral vector comprising in 5' to 3' order: (a) a 5' long terminal repeat region of the structure U3-R-U5; (b) one or more coding sequences, said sequences being inserted into the body of the vector; and (c) a 3' long terminal repeat region comprising a partially deleted U3 region.

The Patent Office asserts that appellant has equated a deleted U3 region with an incomplete U3 region, but contended that this is "incorrect" because claim 1 "do[es] not require an incomplete or defective U3 region" (Final Official Action dated October 26, 2004, at page 9). The Patent Office further asserts that "it is apparent that the appellant wishes to claim a combined deletion/substitution LTR in the mouse mammary tumor virus embodiment of claim 7 (as disclosed in the example of pages 21-22 of the instant

specification; Final Official Action dated October 26, 2004, at pages 9-10). Appellant respectfully submits that this assertion improperly attempts to incorporate into claim 1 a limitation found in the specification.

To elaborate, appellant respectfully submits that the Patent Office appears to suggest that the pMMTVgal vector disclosed on page 21 of the specification shows that appellant intends to claim a retroviral vector with a complete MMTV 3' U3 region. Appellant respectfully submits, however, that it is improper for the Patent Office to attempt to limit the claims to this embodiment. To elaborate, the specification at page 21 states:

> According to the principle set forth above the following specific promoters have been inserted in to the polylinker region [of] the modified BAG vector: several subregions of the Mouse Mammary tumor Virus (MMTV) promoter, including a region that confers responsiveness to glucocorticoid hormones and a region containing an element that directs expression to the mammary gland...

Specification at page 21, lines 1-7 (emphasis added). This passage clearly discloses that it is not necessary that the entire U3 region be inserted into the polylinker. Appellant respectfully submits that the specification clearly indicates that the glucocorticoid hormone response element, the mammary gland-specific region, or both could be cloned into the polylinker to produce a retroviral vector characterized by a partial deletion of the 3' U3 region as recited in claim 1.

Accordingly, appellant respectfully submits that contrary to the Patent Office's assertion, the disclosure of pMMTVgal does not support the contention that appellant wishes to claim a combined deletion/substitution LTR. Appellant respectfully submits that the retroviral vectors of claim 1 are characterized by partial U3 deletions, and that

unlike the disclosure of Couture in view of Faustinella, these deletions are not repaired by substituting the corresponding sequences of the U3 region of another retrovirus into the recited polylinker. Thus, appellant respectfully submits that claim 1 has been distinguished from Couture in view of Faustinella because Couture in view of Faustinella does not teach or suggest a retroviral vector with a partially deleted U3 region. Appellant respectfully requests that the instant rejection be reversed.

A.1.b. There is no motivation to combine Couture with Faustinella

The Patent Office asserts that it would have been obvious to a person of skill in the art at the time the invention was made to modify the vectors of Couture by adding a multiple cloning site of Faustinella because Faustinella shows that multiple cloning sites may be used to insert sequences of choice in a U3 region of a retroviral vector (*see* Final Official Action dated October 26, 2004, at page 4). However, appellant respectfully submits that the Patent Office has misinterpreted Couture in order to arrive at this conclusion. Appellant respectfully submits that Couture does not suggest that "sequences of choice" can be inserted into a U3 region of a retroviral vector, but at best that retroviral vectors can be constructed by swapping corresponding regions of U3 between highly related retroviruses.

As discussed hereinabove, given that this exchange can be accomplished using conserved restriction sites, appellant respectfully submits that there is no motivation to employ a polylinker as disclosed in Faustinella in the Couture vectors, and that the Patent Office has employed impermissible hindsight in proposing the addition of a polylinker to the Couture vectors by combining Couture and Faustinella. Thus, no motivation to combine the references can be found in the references themselves, and

indeed that the only motivation to combine the references is through hindsight reference to the teaching of the instant United States patent application. Accordingly, the Patent Office has not established a *prima facie* case of obviousness of claim 1 over the combination of Couture and Faustinella.

Continuing with the instant rejection, the Patent Office also asserts that Faustinella shows in Figure 1 retroviral vector pS3, which is further asserted to comprise a partial deletion of the 3' U3 region into which a polylinker has been inserted. Appellant respectfully submits, however, that the purpose of Faustinella is to create a self-inactivating (SIN) vector by deleting the promoter/enhancer sequences present within the 3' LTR (*see* Faustinella at page 307). Thus, Faustinella cannot be combined with Couture because to do so would destroy the intended operation of the Faustinella vectors.

To elaborate, appellant respectfully submits that SIN vectors generally, and the SIN vectors of Faustinella in particular, are retroviral vectors that are designed to encode retroviral particles that, after infection of a host cell followed by reverse transcription, are incapable of expressing retroviral genes from promoters normally found in the retroviral LTRs. This is accomplished using one of two general strategies. Typically, a SIN vector lacks the promoter and/or enhancer sequences ordinarily present within the 3' U3 region, such that after reverse transcription, which duplicates the 3' U3 into the 5' LTR, both LTRs lack promoter/enhancer elements.

The second strategy for producing a SIN vector involves producing a 3' U3 that contains a promoter and/or enhancer, but which also includes a coding sequence that is operatively linked to the promoter and/or enhancer in the vector itself. In this case,

upon infection of a host cell the retroviral vectors are reverse transcribed into products that contain LTR promoters, but which are incapable of directing transcription of retroviral genes present within the body of the retrovirus because the transcript generated from the LTR promoter terminates at the 3' end of the operatively linked coding sequence (*i.e.*, terminates before transcribing any coding sequences present in the body of the vector).

Examples of both of these strategies are depicted in Figure 2 of Faustinella. In each of the 11 retroviral vectors disclosed in Figure 2, the promoter originally present in the 3' U3 region is deleted and no new promoter is cloned into the deletion (*see* vectors pS3, pS3TKHygSB, pS3TKHygRB, pS3RSVlucSB, and pS3RSVlucRB) or, if a promoter is cloned into the deletion, an operatively linked coding sequence is also cloned into the deletion (*see* vectors pS3TKHygSL, pS3TKHygRL, pS3TKHygRB-RSVlucSL, pS3TKHygRB-RSVlucRL, pS2RSVlucSL, and pS2RSVlucRL).

Hence, Figure 2 of Faustinella demonstrates that all of the pS3-based vectors are "self-inactivating", meaning that in no case does Faustinella disclose a vector that has a 3' deletion into which a promoter and/or regulator element alone has been inserted. Thus, when taken in its entirety, appellant respectfully submits that Faustinella teaches away from deleting 3' U3 sequences and then introducing a promoter and/or a regulatory sequence alone into the deletion because to do so would destroy the self-inactivation character of the vector that the U3 deletion was designed to create.

The Patent Office contends that "the particular insert used by Faustinella et al. does not directly teach away from use of other inserts, such as the LTR promoter inserted into the U3 region by Couture et al." (Final Official Action at page 10).

Appellant respectfully submits that this contention is inaccurate. As discussed hereinabove, insertion of the U3 region disclosed by Couture into the polylinker of Faustinella would destroy the self-inactivating character of the Faustinella construct. Thus, appellant respectfully submits that the LTR promoter of Couture could not be inserted into the Faustinella polylinker unless a coding sequence was operatively linked thereto. As such, appellant respectfully submits that contrary to the Patent Office's contention, Faustinella indeed does directly teach away from the use of other inserts such as the LTR promoter inserted into the U3 region as disclosed in Couture because to do so would destroy the operation of Faustinella's SIN vector.

Thus, appellant respectfully submits that Faustinella when read as a whole does not suggest the insertion of only a promoter and/or regulatory element(s) into the polylinker present within the 3' U3 deletion. As such, appellant respectfully submits that Faustinella cannot be combined with Couture to suggest a vector with a 3' U3 deletion into which a competent promoter and/or regulatory sequence alone is inserted. On the contrary, appellant respectfully submits that Faustinella can only reasonably be interpreted to teach either a deletion of all or part of the 3' U3 to create a SIN vector, or, if a promoter is cloned into the 3' U3 deletion, a coding sequence must be operatively linked to the promoter in order to retain the benefit of the 3' U3 deletion (*i.e.*, the SIN function).

This is in contrast to the retroviral vectors of claim 1. Appellant respectfully submits that the retroviral vectors of claim 1 are intentionally designed not to be self-inactivating vectors (*see* Specification at page 10, lines 1-3). This is shown by the clause in claim 1 that recites:

> wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous promoter and said heterologous promoter regulating expression of said one or more coding sequences in said target cell[.]

Thus, the promoter that is inserted into the polylinker cloned into the 3' U3 deletion is not operably linked to a coding sequence in the retroviral vector itself, but rather becomes operably linked to a coding sequence present within the body of the vector after reverse transcription. Accordingly, appellant respectfully submits that claim 1 is distinguished over the cited combination of Couture and Faustinella.

Appellant further respectfully submits that the Patent Office has not shown why one of ordinary skill in the art would have read Couture and been motivated to add a polylinker without the benefit of hindsight vision based on appellant's specification, since Couture clearly based the disclosed vectors on replacement of one region of U3 with that of a highly related retrovirus using restriction sites that were common to the various retroviruses or already present in convenient locations. Appellant respectfully submits that the Patent Office has combined the polylinker of Faustinella with the vectors of Couture to address a problem that was neither encountered in, nor suggested by, the vectors disclosed in Couture.

Thus, appellant respectfully submits that there is no motivation to combine the cited references because the element the Patent Office asserts is supplied by Faustinella is one that the skilled artisan would not have been motivated to include in Couture's vectors. Accordingly, appellant respectfully submits that the Patent Office is

employing an impermissible hindsight reconstruction of the references to arrive at the asserted combination.

Therefore, appellant respectfully submits that the combination of the cited references does not suggest the desirability of making the asserted modification. Thus, it is respectfully submitted that no motivation to combine the references can be found and a *prima facie* case of obviousness has not been established.

Summarily, with respect to the instant rejection of independent claim 1 under 35 U.S.C. § 103(a) over Couture in view of Faustinella, appellant respectfully submits that the cited combination does not suffice to create a *prima facie* case of obviousness for several reasons. First, the references do not disclose retroviral vectors that contain partial 3' U3 deletions into which a polylinker and a promoter and/or a regulatory element(s) has been inserted, wherein after infection of a target cell, one or more coding sequences present in the body of the vector becoming operatively linked to the promoter and/or regulatory sequence(s) to regulate expression of one or more coding sequences present within the body of the vector in said target cell. Second, there is no motivation to combine the cited references, because it is only by using impermissible hindsight vision can the references be combined at all.

Accordingly, appellant respectfully submits that the rejection of claim 1 over Couture in view of Faustinella should be reversed.

A.2. Argument for dependent claims 5, 9, 11, 12, 16, 25, 29, 31, and 32

Claims 5, 9, 11, 12, 16, 25, 29, 31, and 32 depend from and further limit claim 1. Accordingly, it is respectfully submitted that the rejection of these claims as being

unpatentable over Couture and Faustinella should be reversed for the reasons stated above with regard to claim 1.

Additionally, with respect to claim 12, appellant respectfully submits that the combination of Couture and Faustinella does not teach or suggest a retroviral vector wherein the marker or therapeutic gene that is present within the body of the vector is a member of the Markush group recited in claim 12 and for which expression is regulated by the promoter and/or regulatory elements cloned into the 3' U3 sequence only after promoter conversion. Rather, appellant respectfully submits that while Couture discloses a neo gene present within the body of the vector, it is operatively linked to an SV40 promoter in the vector.

Thus, the neo gene in the Couture vectors is constitutively expressed in any cell that the retroviral vector enters. This is unlike the neo gene recited in claim 12, which would only be expressed in those cells in which the promoter and/or regulator elements present in the 3' U3 region is active. Accordingly, appellant respectfully submits that the combination of Couture and Faustinella does not teach or suggest the vectors of claim 12 for this additional reason.

A.3. Argument for independent claim 17

The rejection of claim 17 as unpatentable over Couture in view of Faustinella should be reversed.

Claim 17 essentially recites a retroviral vector kit comprising the retroviral vector of claim 1 and a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged. Appellant respectfully submits that the combination of Couture and Faustinella does not

support a rejection of claim 17 under § 103 for the reasons presented hereinabove with respect to claim 1. Particularly, the combination of Couture and Faustinella does not teach or suggest the retroviral vector of claim 1, and as such, does not support an obviousness rejection of a kit that includes the retroviral vector of claim 1, as recited in claim 17.

Furthermore, appellant respectfully submits that since there is no motivation to combine the Couture and Faustinella references as proposed by the Patent Office, the Patent Office has not presented a *prima facie* case of obviousness of claim 17 over Couture and Faustinella.

Accordingly, appellant respectfully submits that the rejection of claim 17 over Couture in view of Faustinella should be reversed.

A.4. Argument for dependent claims 18, 19, 22, 23, and 24

Claims 18, 19, 22, 23, and 24 depend from and further limit claim 17. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture and Faustinella should be reversed for the reasons stated above with regard to claims 1 and 17.

A.5. Argument for independent claim 28

The rejection of claim 28 as unpatentable over Couture in view of Faustinella should be reversed.

Claim 28 essentially recites a producer cell line comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be packaged. Appellant respectfully submits that the combination of Couture and Faustinella does not support a rejection of claim 28 under § 103 for the reasons

presented hereinabove with respect to claim 1. Particularly, the combination of Couture and Faustinella does not teach or suggest the retroviral vector of claim 1, and as such, does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be packaged, as recited in claim 28.

Furthermore, appellant respectfully submits that since there is no motivation to combine the Couture and Faustinella references as proposed by the Patent Office, the Patent Office has not presented a *prima facie* case of obviousness of claim 28 over Couture and Faustinella.

Accordingly, appellant respectfully submits that the rejection of claim 28 over Couture in view of Faustinella should be reversed.

A.6. Argument for dependent claims 20 and 21

The rejection of claims 20 and 21 as unpatentable over Couture in view of Faustinella should be reversed.

Claims 20 and 21 depend from and further limit claim 28. Claims 20 and 21 essentially recite methods for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells by infecting the cells with recombinant retroviruses produced by the producer cell line of claim 28 (claim 20), wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters, and combinations thereof (claim 21).

Appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 20 and 21 for the reasons presented hereinabove

with respect to claim 1 and claim 28. Particularly, the combination of Couture and Faustinella does not teach or suggest the retroviral vector of claim 1, and as such, does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be packaged, as recited in claims 20 and 21.

Furthermore, appellant respectfully submits that since there is no motivation to combine the Couture and Faustinella references as proposed by the Patent Office, the Patent Office has not presented a *prima facie* case of obviousness of claims 20 and 21 over Couture and Faustinella.

Accordingly, it is respectfully submitted that the rejection of claims 20 and 21 as being unpatentable over Couture and Faustinella should be reversed.

A.7. Argument for independent claim 56

The rejection of claim 56 as unpatentable over Couture in view of Faustinella should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture and Faustinella does not teach or suggest the subject matter of these claims.

Claim 56 essentially recites the retroviral vector of claim 1, wherein the heterologous promoter is a heterologous retroviral promoter. Attention is directed to the arguments presented hereinabove with respect to the use of MMTV regulatory elements in the vector of claim 1. Given that the claimed retroviral vector need not employ the

entire U3 region of the heterologous retrovirus to include the heterologous promoter, appellant respectfully submits that the combination of Couture and Faustinella does not teach or suggest the retroviral vector of claim 56.

Furthermore, appellant respectfully submits that there is no motivation to combine Couture and Faustinella as proposed by the Patent Office for the reasons presented hereinabove. As such, appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 56.

Accordingly, appellant respectfully submits that the rejection of claim 56 over Couture in view of Faustinella should be reversed.

A.8. Argument for dependent claims 57, 59, 61, 62, 65, 72, 77, and 78

Claims 57, 59, 61, 62, 65, 72, 77, and 78 depend from and further limit claim 56. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture and Faustinella should be reversed for the reasons stated above with regard to claims 1 and 56.

Additionally, concerning claim 62, appellant respectfully submits that the combination of Couture and Faustinella does not teach or suggest a retroviral vector wherein the marker or therapeutic gene that is present within the body of the vector is a member of the Markush group recited in claim 62 and for which expression is regulated by the promoter and/or regulatory elements cloned into the 3' U3 sequence only after promoter conversion. Rather, appellant respectfully submits that while Couture discloses a neo gene present within the body of the vector, it is operatively linked to an SV40 promoter in the vector.

Thus, the neo gene in the Couture vectors is constitutively expressed in any cell that the retroviral vector enters. This is unlike the neo gene recited in claim 62, which would only be expressed in those cells in which the promoter and/or regulator elements present in the 3' U3 region is active. Accordingly, appellant respectfully submits that the combination of Couture and Faustinella does not teach or suggest the vectors of claim 62 for this additional reason.

A.9. Argument for independent claim 66

The rejection of claim 66 as unpatentable over Couture in view of Faustinella should be reversed.

Claim 66 essentially recites a retroviral vector kit comprising the retroviral vector of claim 56 and a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged. Appellant respectfully submits that since the combination of Couture and Faustinella does not teach or suggest the retroviral vector of claim 56, the combination does not support an obviousness rejection of a kit comprising the retroviral vector of claim 56, as recited in claim 66.

Furthermore, appellant respectfully submits that since there is no motivation to combine the Couture and Faustinella references as proposed by the Patent Office, the Patent Office has not presented a *prima facie* case of obviousness of claim 66 over Couture and Faustinella.

Accordingly, appellant respectfully submits that the rejection of claim 66 over Couture in view of Faustinella should be reversed.

A.10. Argument for dependent claims 67-71

Claims 67-71 depend from and further limit claim 66. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture and Faustinella should be reversed for the reasons stated above with regard to claims 1 and 66.

A.11. Argument for independent claim 74

The rejection of claim 74 as unpatentable over Couture in view of Faustinella should be reversed.

Claim 74 essentially recites a producer cell line comprising the retroviral vector of claim 56 and a DNA construct coding for proteins required for the retroviral vector to be packaged. Appellant respectfully submits that since the combination of Couture and Faustinella does not teach or suggest the retroviral vector of claim 56, the combination does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 56, as recited in claim 74.

Furthermore, appellant respectfully submits that there is no motivation to combine Couture and Faustinella as proposed by the Patent Office for the reasons presented hereinabove. As such, appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 74.

Accordingly, appellant respectfully submits that the rejection of claim 74 over Couture in view of Faustinella should be reversed.

A.12. Argument for dependent claims 75 and 76

Claims 75 and 76 depend from and further limit claim 74. Claims 75 and 76 essentially recite methods for introducing homologous or heterologous nucleotide

sequences into cells in an animal or cultured cells by infecting the cells with recombinant retroviruses produced by the producer cell line of claim 74 (claim 75), wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters, and combinations thereof (claim 76).

Appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 75 and 76 for the reasons presented hereinabove with respect to claim 56 and claim 74. Particularly, the combination of Couture and Faustinella does not teach or suggest the retroviral vector of claim 56, and as such, does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 56 and a DNA construct coding for proteins required for the retroviral vector to be packaged, as recited in claims 75 and 76.

Furthermore, appellant respectfully submits that since there is no motivation to combine the Couture and Faustinella references as proposed by the Patent Office for the reasons presented hereinabove, the Patent Office has not presented a *prima facie* case of obviousness of claims 75 and 76 over Couture and Faustinella.

Accordingly, it is respectfully submitted that the rejection of claims 75 and 76 as being unpatentable over Couture and Faustinella should be reversed.

B. Rejection of claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78 under 35 U.S.C. § 103(a) as being unpatentable over Couture in view of Faustinella, and further in view of Mee

B.1. Argument for independent claim 1

The rejection of claim 1 as unpatentable over Couture in view of Faustinella, and further in view of Mee, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture, Faustinella, and Mee does not teach or suggest the subject matter of these claims.

The Patent Office bases this rejection on those contentions made in reference to the Couture and Faustinella references in combination with the asserted disclosure in Mee of a retroviral vector comprising an MMTV LTR. From this combination, the Patent Office contends that it would have been obvious to modify the vector of Couture in view of Faustinella by insertion of an MMTV promoter region in a deleted 3' U3 region of a retroviral vector because Mee shows that their LTR promoter may be used to manipulate gene expression in a variety of cell types.

However, appellant respectfully submits that the addition of the Mee reference does not cure the deficiencies of the combination of Couture and Faustinella outlined above, which are incorporated herein by reference. To reiterate, Couture and Faustinella fail to suggest a retroviral vector characterized by an incomplete 3' U3

region and a heterologous promoter that upon promoter conversion becomes operatively linked to a gene of interest encoded within the body of the vector.

This deficiency is not cured by the addition of the Mee reference. Particularly, appellant respectfully submits that Mee discloses self-inactivating vectors, which have been distinguished from the vectors of claim 1 above. As clearly stated on page 290 of Mee, the vectors were designed such that the gene of interest was cloned "such that a start codon in the inserted sequence will be the first AUG downstream of the *tsp* of the MMTV *HRE* promoter".

Thus, Mee discloses a plasmid vector wherein the MMTV promoter element (the HRE) is operatively linked to the gene it is to regulate from the outset. Other genes that are disclosed in Mee, including the *aph* gene and the *cat* gene, were also cloned so that they were operatively linked to their promoters. Thus, even assuming *arguendo* that Mee discloses the use of an MMTV LTR for the manipulation of gene expression in a variety of cell types, appellant respectfully submits that it does not provide the missing suggestion of Couture and Faustinella of a retroviral vector characterized by an incomplete 3' U3 region and a heterologous promoter that upon promoter conversion becomes operatively linked to a gene of interest to which it was not operatively linked prior to the promoter conversion event.

Furthermore, appellant respectfully submits that there is no motivation to combine Couture and Faustinella as proposed by the Patent Office for the reasons set forth hereinabove, and further that there is no motivation to combine Couture and Faustinella with Mee. Summarily, appellant respectfully submits that Couture does not teach a vector with a 3' U3 deletion nor does it suggest the need for using a polylinker

for cloning purposes, and Faustinella and Mee teach against deleting 3' U3 sequences and then introducing a promoter and/or regulatory sequences alone into the deletion because to do so would destroy the self-inactivation character of the vectors disclosed in each of these references.

As such, appellant respectfully submits that the instant rejection is based on an impermissible hindsight reconstruction of the cited Couture, Faustinella, and Mee references, and thus the Patent Office has not presented a *prima facie* case of obviousness of claim 1.

As a result, appellant respectfully submits that the rejection of claim 1 over the combination of Couture and Faustinella, and further in view of Mee, should be reversed.

B.2. Argument for dependent claims 5, 7, 9, 11, 12, 16, 25, 29, 31, and 32

Claims 5, 7, 9, 11, 12, 16, 25, 29, 31, and 32 depend from and further limit claim 1. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture and Faustinella, and further in view of Mee, should be reversed for the reasons stated above with regard to claim 1.

Additionally, with respect to claim 12, appellant respectfully submits that the combination of Couture and Faustinella and further in view of Mee does not teach or suggest a retroviral vector wherein the marker or therapeutic gene that is present within the body of the vector is a member of the Markush group recited in claim 12 and for which expression is regulated by the promoter and/or regulatory elements cloned into the 3' U3 sequence only after promoter conversion. Rather, appellant respectfully submits that while Couture discloses a neo gene present within the body of the vector, it is operatively linked to an SV40 promoter in the vector.

Thus, the neo gene in the Couture vectors is constitutively expressed in any cell that the retroviral vector enters. This is unlike the neo gene recited in claim 12, which would only be expressed in those cells in which the promoter and/or regulator elements present in the 3' U3 region is active.

Accordingly, appellant respectfully submits that the combination of Couture and Faustinella and further in view of Mee does not teach or suggest the vectors of claim 12 for this additional reason.

B.3. Argument for independent claim 17

The rejection of claim 17 as unpatentable over Couture in view of Faustinella and further in view of Mee should be reversed.

Claim 17 essentially recites a retroviral vector kit comprising the retroviral vector of claim 1 and a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged. Appellant respectfully submits that the combination of Couture and Faustinella and further in view of Mee does not support a rejection of claim 17 under § 103 for the reasons presented hereinabove with respect to claim 1. Particularly, the combination of Couture and Faustinella in view of Mee does not teach or suggest the retroviral vector of claim 1, and as such, does not support an obviousness rejection of a kit that includes the retroviral vector of claim 1, as recited in claim 17.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee references as proposed by the Patent Office. As such, the Patent Office has not

presented a *prima facie* case of obviousness of claim 17 over Couture and Faustinella and further in view of Mee.

Accordingly, appellant respectfully submits that the rejection of claim 17 over Couture in view of Faustinella and further in view of Mee should be reversed.

B.4. Argument for dependent claims 18, 19, 22, 23, and 24

Claims 18, 19, 22, 23, and 24 depend from and further limit claim 17. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture and Faustinella, and further in view of Mee, should be reversed for the reasons stated above with regard to claims 1 and 17.

B.5. Argument for independent claim 28

The rejection of claim 28 as unpatentable over Couture in view of Faustinella, and further in view of Mee, should be reversed.

Claim 28 essentially recites a producer cell line comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be packaged. Appellant respectfully submits that the combination of Couture and Faustinella and further in view of Mee does not support a rejection of claim 28 under § 103 for the reasons presented hereinabove with respect to claim 1. Particularly, the combination of Couture and Faustinella and further in view of Mee does not teach or suggest the retroviral vector of claim 1, and as such, does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be packaged as recited in claim 28.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee references as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 28 over Couture and Faustinella and further in view of Mee.

Accordingly, appellant respectfully submits that the rejection of claim 28 over Couture in view of Faustinella and further in view of Mee should be reversed.

B.6. Argument for dependent claims 20 and 21

The rejection of claims 20 and 21 as unpatentable over Couture in view of Faustinella and further in view of Mee should be reversed.

Claims 20 and 21 depend from and further limit claim 28. Claims 20 and 21 essentially recite methods for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells by infecting the cells with recombinant retroviruses produced by the producer cell line of claim 28 (claim 20), wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters, and combinations thereof (claim 21).

Appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 20 and 21 for the reasons presented hereinabove with respect to claim 1 and claim 28. Particularly, the combination of Couture and Faustinella and further in view of Mee does not teach or suggest the retroviral vector of claim 1, and as such, does not support an obviousness rejection of a producer cell line

comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be packaged as recited in claims 20 and 21.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee references as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claims 21 and 22 over Couture and Faustinella and further in view of Mee.

Accordingly, it is respectfully submitted that the rejection of claims 20 and 21 as being unpatentable over Couture and Faustinella and further in view of Mee should be reversed.

B.7. Argument for independent claim 56

The rejection of claim 56 as unpatentable over Couture in view of Faustinella, and further in view of Mee, should be reversed.

Claim 56 essentially recites a producer cell line comprising the retroviral vector of claim 1, wherein the heterologous promoter is a heterologous retroviral promoter, and a DNA construct coding for proteins required for the retroviral vector to be packaged. Appellant respectfully submits that the combination of Couture and Faustinella and further in view of Mee does not support a rejection of claim 56 under § 103 for the reasons presented hereinabove with respect to claim 1. Particularly, the combination of Couture and Faustinella and further in view of Mee does not teach or suggest the retroviral vector of claim 1, and as such, does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 1, wherein the heterologous

promoter is a heterologous retroviral promoter, and a DNA construct coding for proteins required for the retroviral vector to be packaged, as recited in claim 56.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee references as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 56 over Couture and Faustinella and further in view of Mee.

Accordingly, appellant respectfully submits that the rejection of claim 56 over Couture in view of Faustinella and Mee should be reversed.

B.8. Argument for dependent claims 57, 58, 59, 61, 62, 65, 72, 77, and 78

Claims 57, 59, 61, 62, 65, 72, 77, and 78 depend from and further limit claim 56. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture and Faustinella and further in view of Mee should be reversed for the reasons stated above with regard to claims 1 and 56.

Additionally, with respect to claim 62, appellant respectfully submits that the combination of Couture, Faustinella, and Mee does not teach or suggest a retroviral vector wherein the marker or therapeutic gene that is present within the body of the vector is a member of the Markush group recited in claim 62 and for which expression is regulated by the promoter and/or regulatory elements cloned into the 3' U3 sequence only after promoter conversion. Rather, appellant respectfully submits that while Couture discloses a neo gene present within the body of the vector, it is operatively linked to an SV40 promoter in the vector.

Thus, the neo gene in the Couture vectors is constitutively expressed in any cell that the retroviral vector enters. This is unlike the neo gene recited in claim 62, which would only be expressed in those cells in which the promoter and/or regulator elements present in the 3' U3 region is active. Accordingly, appellant respectfully submits that the combination of Couture, Faustinella, and Mee does not teach or suggest the vectors of claim 62 for this additional reason.

B.9. Argument for independent claim 66

The rejection of claim 66 as unpatentable over Couture in view of Faustinella and further in view of Mee should be reversed.

Claim 66 essentially recites a retroviral vector kit comprising the retroviral vector of claim 56 and a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged. Appellant respectfully submits that since the combination of Couture, Faustinella, and Mee does not teach or suggest the retroviral vector of claim 56, the combination does not support an obviousness rejection of a kit comprising the retroviral vector of claim 56, as recited in claim 66.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee references as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 66 over Couture and Faustinella and further in view of Mee.

Accordingly, appellant respectfully submits that the rejection of claim 66 over Couture in view of Faustinella and further in view of Mee should be reversed.

B.10. Argument for dependent claims 67-71

Claims 67-71 depend from and further limit claim 66. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture, Faustinella, and Mee should be reversed for the reasons stated above with regard to claims 1 and 66.

B.11. Argument for independent claim 74

The rejection of claim 74 as unpatentable over Couture in view of Faustinella, and further in view of Mee, should be reversed.

Claim 74 essentially recites a producer cell line comprising the retroviral vector of claim 56 and a DNA construct coding for proteins required for the retroviral vector to be packaged. Appellant respectfully submits that since the combination of Couture and Faustinella and further in view of Mee does not teach or suggest the retroviral vector of claim 56, the combination does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 56, as recited in claim 74.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee references as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 74 over Couture and Faustinella and further in view of Mee.

Accordingly, appellant respectfully submits that the rejection of claim 74 over Couture in view of Faustinella and further in view of Mee should be reversed.

B.12. Argument for dependent claims 75 and 76

Claims 75 and 76 depend from and further limit claim 74. Claims 75 and 76 essentially recite methods for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells by infecting the cells with recombinant retroviruses produced by the producer cell line of claim 74 (claim 75), wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters, and combinations thereof (claim 76).

Appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 75 and 76 for the reasons presented hereinabove with respect to claim 56 and claim 74. Particularly, the combination of Couture and Faustinella and further in view of Mee does not teach or suggest the retroviral vector of claim 56, and as such, does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 56 and a DNA construct coding for proteins required for the retroviral vector to be packaged, as recited in claims 75 and 76.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee references as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claims 75 and 76 over Couture and Faustinella and further in view of Mee.

Accordingly, it is respectfully submitted that the rejection of claims 75 and 76 as being unpatentable over Couture and Faustinella and further in view of Mee should be reversed.

C. Rejection of claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-36, 38, 39, 42-49, and 51-55 under 35 U.S.C. § 103(a) as being unpatentable over Couture in view of Faustinella, and further in view of Mehigh

C.1. Argument for independent claim 1

The rejection of these claims as unpatentable over Couture in view of Faustinella, and further in view of Mehigh, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture, Faustinella, and Mehigh does not teach or suggest the subject matter of these claims.

The Patent Office bases the instant rejection upon the assertions made in reference to the Couture and Faustinella references, in combination with the asserted disclosure in Mehigh of a retroviral vector comprising a WAP promoter. From this combination, the Patent Office contends that it would have been obvious to modify the vector of Couture in view of Faustinella by insertion of a WAP promoter region in a deleted 3' U3 region of a retroviral vector because Mehigh shows that such vectors are inducibly expressed and may allow for increased milk production in cattle.

The discussions presented hereinabove with regard to the deficiencies of the Couture and Faustinella references are incorporated herein. Appellant respectfully submits that Mehigh does not cure these deficiencies because Mehigh does not teach or suggest the construction of a vector that contains a partially deleted U3 region and

undergoes promoter conversion to operatively link the disclosed promoters to the genes of interest. As is clearly stated in the Abstract of Mehigh, "the gene encoding synthetic bGRF... was fused to the whey acidic protein promoter (WAP) or the mouse mammary tumor virus promoter (MMTV)" (emphasis added). Consequently, it is clear from the disclosure that at best Mehigh teaches the use of the WAP and MMTV promoters to control the expression of linked genes.

Furthermore, appellant respectfully submits that there is no motivation to combine Couture and Faustinella as proposed by the Patent Office for the reasons set forth hereinabove, and further that there is no motivation to combine Couture and Faustinella with Mehigh. Summarily, appellant respectfully submits that Couture does not teach a vector with a 3' U3 deletion nor does it suggest the need for using a polylinker for cloning purposes, and Faustinella teaches against deleting 3' U3 sequences and then introducing a promoter and/or regulatory sequences alone into the deletion because to do so would destroy the self-inactivation character of the vector that the U3 deletion was designed to create. Further, it is clear from the disclosure that at best Mehigh teaches the use of the WAP and MMTV promoters to control the expression of linked genes.

As such, appellant respectfully submits that the instant rejection is based on an impermissible hindsight reconstruction of the cited Couture and Faustinella references, and also on an impermissible hindsight reconstruction of the cited Couture, Faustinella, and Mehigh references, and thus the Patent Office has not presented a *prima facie* case of obviousness of claim 1.

As a result, appellant respectfully submits that the rejection of claim 1 over the combination of Couture and Faustinella, and further in view of Mehigh, should be reversed.

C.2. Argument for dependent claims 5, 7, 9, 11, 12, 15, 16, 25, 29, 31, and 32

Claims 5, 7, 9, 11, 12, 16, 25, 29, 31, and 32 depend from and further limit claim 1. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture and Faustinella, and further in view of Mehigh, should be reversed for the reasons stated above with regard to claim 1.

Additionally, with respect to claim 12, appellant respectfully submits that the combination of Couture and Faustinella and further in view of Mehigh does not teach or suggest a retroviral vector wherein the marker or therapeutic gene that is present within the body of the vector is a member of the Markush group recited in claim 12 and for which expression is regulated by the promoter and/or regulatory elements cloned into the 3' U3 sequence only after promoter conversion. Rather, appellant respectfully submits that while Couture discloses a neo gene present within the body of the vector, it is operatively linked to an SV40 promoter in the vector.

Thus, the neo gene in the Couture vectors is constitutively expressed in any cell that the retroviral vector enters. This is unlike the neo gene recited in claim 12, which would only be expressed in those cells in which the promoter and/or regulator elements present in the 3' U3 region is active.

Accordingly, appellant respectfully submits that the combination of Couture and Faustinella and further in view of Mehigh does not teach or suggest the vectors of claim 12 for this additional reason.

C.3. Argument for independent claim 17

The rejection of claim 17 as unpatentable over Couture in view of Faustinella and further in view of Mehigh should be reversed.

Claim 17 essentially recites a retroviral vector kit comprising the retroviral vector of claim 1 and a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged. Appellant respectfully submits that the combination of Couture and Faustinella and further in view of Mehigh does not support a rejection of claim 17 under § 103 for the reasons presented hereinabove with respect to claim 1. Particularly, the combination of Couture and Faustinella in view of Mehigh does not teach or suggest the retroviral vector of claim 1, and as such, does not support an obviousness rejection of a kit that includes the retroviral vector of claim 1, as recited in claim 17.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mehigh references as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 17 over Couture and Faustinella and further in view of Mehigh.

Accordingly, appellant respectfully submits that the rejection of claim 17 over Couture in view of Faustinella and further in view of Mehigh should be reversed.

C.4. Argument for dependent claims 18, 19, 22, 23, and 24

Claims 18, 19, 22, 23, and 24 depend from and further limit claim 17. Accordingly, it is respectfully submitted that the rejection of these claims as being

unpatentable over Couture and Faustinella, and further in view of Mehigh, should be reversed for the reasons stated above with regard to claims 1 and 17.

C.5. Argument for independent claim 28

The rejection of claim 28 as unpatentable over Couture in view of Faustinella, and further in view of Mehigh, should be reversed.

Claim 28 essentially recites a producer cell line comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be packaged. Appellant respectfully submits that the combination of Couture and Faustinella and further in view of Mehigh does not support a rejection of claim 28 under § 103 for the reasons presented hereinabove with respect to claim 1. Particularly, the combination of Couture and Faustinella and further in view of Mehigh does not teach or suggest the retroviral vector of claim 1, and as such, does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be packaged, as recited in claim 28.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mehigh references as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 28 over Couture and Faustinella and further in view of Mehigh.

Accordingly, appellant respectfully submits that the rejection of claim 28 over Couture in view of Faustinella and further in view of Mehigh should be reversed.

C.6. Argument for dependent claims 20 and 21

The rejection of claims 20 and 21 as unpatentable over Couture in view of Faustinella and further in view of Mehigh should be reversed.

Claims 20 and 21 depend from and further limit claim 28. Claims 20 and 21 essentially recite methods for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells by infecting the cells with recombinant retroviruses produced by the producer cell line of claim 28 (claim 20), wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters, and combinations thereof (claim 21).

Appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 20 and 21 for the reasons presented hereinabove with respect to claim 1 and claim 28. Particularly, the combination of Couture and Faustinella and further in view of Mehigh does not teach or suggest the retroviral vector of claim 1, and as such, does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be packaged, as recited in claims 20 and 21.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mehigh references as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claims 20 and 21 over Couture and Faustinella and further in view of Mehigh.

Accordingly, it is respectfully submitted that the rejection of claims 20 and 21 as being unpatentable over Couture and Faustinella and further in view of Mehigh should be reversed.

C.7. Argument for independent claim 33

The rejection of claim 33 as unpatentable over Couture in view of Faustinella, and further in view of Mehigh, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture, Faustinella, and Mehigh does not teach or suggest the subject matter of these claims.

Claim 33 essentially recites the retroviral vector of claim 1, wherein the heterologous promoter is a promoter from a cellular gene. Appellant respectfully submits that since the combination of Couture, Faustinella, and Mehigh does not teach or suggest the retroviral vector of claim 1, the combination does not support an obviousness rejection of a retroviral vector of claim 1, wherein the heterologous promoter is a cellular promoter, as recited in claim 33.

Additionally, appellant respectfully submits that Mehigh appears to be relied in for its teaching of the whey acidic protein and MMTV promoters. However, appellant respectfully submits that Mehigh does not teach that these promoters are located in the 3' U3 region and control transcription of coding sequences present in the body of the vector after promoter conversion. With reference to Figure 3 of Mehigh, it is clear that

the disclosure of Mehigh is limited to employing these promoters already operably linked to a coding sequence in the body of the vector.

Furthermore, appellant respectfully submits that there is no motivation to combine Couture, Faustinella, and Mehigh as proposed by the Patent Office for the reasons presented hereinabove. Summarily, appellant respectfully submits that Couture does not teach a vector with a 3' U3 deletion nor does it suggest the need for using a polylinker for cloning purposes, and Faustinella teaches against deleting 3' U3 sequences and then introducing a promoter and/or regulatory sequences alone into the deletion because to do so would destroy the self-inactivation character of the vector that the U3 deletion was designed to create. Additionally, it is clear that the disclosure of Mehigh is limited to employing these promoters already operably linked to a coding sequence in the body of the vector.

As such, appellant respectfully submits that the instant rejection is based on an impermissible hindsight reconstruction of the cited Couture, Faustinella, and Mehigh references, and thus the Patent Office has not presented a *prima facie* case of obviousness of claim 33.

Accordingly, appellant respectfully submits that the rejection of claim 33 over Couture in view of Faustinella, and further in view of Mehigh, should be reversed.

C.8. Argument for dependent claims 34-36, 38, 39, 42, 49, 54, and 55

Claims 34-36, 38, 39, 42, 49, 54, and 55 depend from and further limit claim 33. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture, Faustinella, and Mehigh should be reversed for the reasons stated above with regard to claims 1 and 33.

Additionally, with respect to claim 39, appellant respectfully submits that the combination of Couture and Faustinella does not teach or suggest a retroviral vector wherein the marker or therapeutic gene that is present within the body of the vector is a member of the Markush group recited in claim 39 and for which expression is regulated by the promoter and/or regulatory elements cloned into the 3' U3 sequence only after promoter conversion. Rather, appellant respectfully submits that while Couture discloses a neo gene present within the body of the vector, it is operatively linked to an SV40 promoter in the vector.

Thus, the neo gene in the Couture vectors is constitutively expressed in any cell that the retroviral vector enters. This is unlike the neo gene recited in claim 39, which would only be expressed in those cells in which the promoter and/or regulator elements present in the 3' U3 region is active. Accordingly, appellant respectfully submits that the combination of Couture, Faustinella, and Mehigh does not teach or suggest the vectors of claim 39 for this additional reason.

C.9. Argument for independent claim 43

The rejection of claim 43 as unpatentable over Couture in view of Faustinella, and further in view of Mehigh, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submit that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture, Faustinella, and Mehigh does not teach or suggest the subject matter of these claims.

Claim 43 essentially recites a retroviral vector kit comprising the retroviral vector of claim 33 and a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged. Appellant respectfully submits that since the combination of Couture, Faustinella, and Mehigh does not teach or suggest the retroviral vector of claim 33, the combination does not support an obviousness rejection of a kit comprising the retroviral vector of claim 33, as recited in claim 43.

Furthermore, appellant respectfully submits that there is no motivation to combine Couture, Faustinella, and Mehigh as proposed by the Patent Office for the reasons presented hereinabove. Summarily, appellant respectfully submits that Couture does not teach a vector with a 3' U3 deletion nor does it suggest the need for using a polylinker for cloning purposes, and Faustinella teaches against deleting 3' U3 sequences and then introducing a promoter and/or regulatory sequences alone into the deletion because to do so would destroy the self-inactivation character of the vector that the U3 deletion was designed to create. Additionally, it is clear that the disclosure of Mehigh is limited to employing these promoters already operably linked to a coding sequence in the body of the vector.

As such, appellant respectfully submits that the instant rejection is based on an impermissible hindsight reconstruction of the cited Couture, Faustinella, and Mehigh references, and thus the Patent Office has not presented a *prima facie* case of obviousness of claim 43.

Accordingly, appellant respectfully submits that the rejection of claim 43 over Couture in view of Faustinella, and further in view of Mehigh, should be reversed.

C.10. Argument for dependent claims 44-48

Claims 44-48 depend from and further limit claim 43. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture, Faustinella, and Mehigh should be reversed for the reasons stated above with regard to claims 1 and 43.

C.11. Argument for independent claim 51

The rejection of claim 51 as unpatentable over Couture in view of Faustinella, and further in view of Mehigh, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture, Faustinella, and Mehigh does not teach or suggest the subject matter of these claims.

Claim 51 essentially recites a producer cell line comprising the retroviral vector of claim 33 and a DNA construct coding for proteins required for the retroviral vector to be packaged. Appellant respectfully submits that since the combination of Couture, Faustinella, and Mehigh does not teach or suggest the retroviral vector of claim 33, the combination does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 33, as recited in claim 51.

Furthermore, appellant respectfully submits that there is no motivation to combine Couture, Faustinella, and Mehigh as proposed by the Patent Office for the reasons presented hereinabove. Summarily, appellant respectfully submits that

Couture does not teach a vector with a 3' U3 deletion nor does it suggest the need for using a polylinker for cloning purposes, and Faustinella teaches against deleting 3' U3 sequences and then introducing a promoter and/or regulatory sequences alone into the deletion because to do so would destroy the self-inactivation character of the vector that the U3 deletion was designed to create. Additionally, it is clear that the disclosure of Mehigh is limited to employing these promoters already operably linked to a coding sequence in the body of the vector.

As such, appellant respectfully submits that the instant rejection is based on an impermissible hindsight reconstruction of the cited Couture, Faustinella, and Mehigh references, and thus the Patent Office has not presented a *prima facie* case of obviousness of claim 51.

Accordingly, appellant respectfully submits that the rejection of claim 51 over Couture in view of Faustinella, and further in view of Mehigh, should be reversed.

C.12. Argument for dependent claims 52 and 53

Claims 52 and 53 depend from and further limit claim 51. Claims 52 and 53 essentially recite methods for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells by infecting the cells with recombinant retroviruses produced by the producer cell line of claim 51 (claim 52), wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters, and combinations thereof (claim 53).

Appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claims 52 and 53 for the reasons presented hereinabove

with respect to claim 33 and claim 51. Particularly, the combination of Couture and Faustinella and further in view of Mehigh does not teach or suggest the retroviral vector of claim 33, or the producer cell line comprising the retroviral vector of claim 33 and a DNA construct coding for proteins required for the retroviral vector to be packaged as recited in claim 51. As a result, appellant respectfully submits that the combination of Couture and Faustinella in view of Mehigh does not support an obviousness rejection of claims to methods of using a retroviral vector of claim 33 produced by the producer cell line of claim 51 as recited in claims 52 and 53.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mehigh references as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claims 52 and 53 over Couture, Faustinella, and Mehigh.

Accordingly, it is respectfully submitted that the rejection of claims 52 and 53 as being unpatentable over Couture and Faustinella and further in view of Mehigh should be reversed.

D. Rejection of claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-36, 38, 39, 42-49, and 51-55 under 35 U.S.C. § 103(a) as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh, as further evidenced by Miller and Panganiban

D.1. Argument for independent claim 1

The rejection of these claims as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, does not teach or suggest the subject matter of these claims.

In addition to the assertions made with respect to the previously discussed obviousness rejections, the Patent Office asserts that Miller and Panganiban disclose retroviral vectors with deletions of the gag, pol, and env genes (Miller) and that the 3' end of the pol gene encodes the int locus, which is required for integration of the reverse transcribed retroviral genome to form a provirus. Appellant respectfully submits, however, that even assuming *arguendo* that the Patent Office's characterizations of the Miller and Panganiban references are correct, these references do not cure the deficiencies discussed hereinabove for the combination of Couture and Faustinella, optionally in combination with Mee or Mehigh.

Appellant respectfully submits that Couture and Faustinella are asserted to suggest a retroviral vector having an incomplete 3' U3 and a polylinker into which a heterologous promoter is inserted that upon promoter conversion becomes operatively linked to a gene encoded within the body of the vector. As discussed in greater detail hereinabove, these references do not in fact suggest a vector of this particular design. Miller and Panganiban do not cure this deficiency. Indeed, the disclosures of Miller and Panganiban are limited to vectors containing modifications of retroviral protein genes or packaging signals (Miller) and/or the identification of the location of the int locus. The vectors do not include 3' U3 deletions, heterologous promoters, and polylinkers located within the 3' LTR. Thus, Miller and Panganiban do not cure the deficiencies of Couture and Faustinella, and as such, the recited combination cannot be deemed to suggest the presently claimed subject matter.

Furthermore, appellant respectfully submits that there is no motivation to combine Couture and Faustinella with Mee or Mehigh based on the disclosure of Miller and Panganiban as proposed by the Patent Office for the reasons presented hereinabove. Summarily, appellant respectfully submits that Couture does not teach a vector with a 3' U3 deletion nor does it suggest the need for using a polylinker for cloning purposes, and Faustinella and Mee teach against deleting 3' U3 sequences and then introducing a promoter and/or regulatory sequences alone into the deletion because to do so would destroy the self-inactivation character of the vectors disclosed therein. Additionally, it is clear that the disclosure of Mehigh is limited to employing these promoters already operably linked to a coding sequence in the body of the vector. Further, the disclosures of Miller and Panganiban are limited to vectors containing

modifications of retroviral protein genes or packaging signals (Miller) and/or the identification of the location of the int locus. The vectors do not include 3' U3 deletions, heterologous promoters, and polylinkers located within the 3' LTR.

As such, appellant respectfully submits that the instant rejection is based on an impermissible hindsight reconstruction of the cited Couture, Faustinella, Mee, Mehigh, Miller, and Panganiban references, and thus the Patent Office has not presented a *prima facie* case of obviousness of claim 1.

Accordingly, appellant respectfully requests that the obviousness rejection of claims 1 over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban be reversed.

D.2. Argument for dependent claims 5, 7, 9, 11, 12, 15, 16, 25, 29, 31, and 32

Claims 5, 7, 9, 11, 12, 16, 25, 29, 31, and 32 depend from and further limit claim 1. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed for the reasons stated above with regard to claim 1.

Additionally, with respect to claim 12, appellant respectfully submits that the combination of Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, does not teach or suggest a retroviral vector wherein the marker or therapeutic gene that is present within the body of the vector is a member of the Markush group recited in claim 12 and for which expression is regulated by the promoter and/or regulatory elements cloned into the 3' U3 sequence only after promoter conversion. Rather, appellant respectfully submits that while Couture

discloses a neo gene present within the body of the vector, it is operatively linked to an SV40 promoter in the vector.

Thus, the neo gene in the Couture vectors is constitutively expressed in any cell that the retroviral vector enters. This is unlike the neo gene recited in claim 12, which would only be expressed in those cells in which the promoter and/or regulator elements present in the 3' U3 region is active.

Accordingly, appellant respectfully submits that the combination of Couture and Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban does not teach or suggest the vectors of claim 12 for this additional reason.

D.3. Argument for independent claim 17

The rejection of claim 17 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed.

Claim 17 essentially recites a retroviral vector kit comprising the retroviral vector of claim 1 and a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged. Appellant respectfully submits that the combination of Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, does not support a rejection of claim 17 under § 103 for the reasons presented hereinabove with respect to claim 1. Particularly, the combination of Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, does not teach or suggest the retroviral vector of claim 1, and as such, does not support an

obviousness rejection of a kit that includes the retroviral vector of claim 1, as recited in claim 17.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 17 over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban.

Accordingly, appellant respectfully submits that the rejection of claim 17 over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed.

D.4. Argument for dependent claims 18, 19, 22, 23, and 24

Claims 18, 19, 22, 23, and 24 depend from and further limit claim 17. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed for the reasons stated above with regard to claims 1 and 17.

D.5. Argument for independent claim 28

The rejection of claim 28 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed.

Claim 28 essentially recites a producer cell line comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be

packaged. Appellant respectfully submits that the combination of Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, does not support a rejection of claim 28 under § 103 for the reasons presented hereinabove with respect to claim 1. Particularly, the combination of Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, does not teach or suggest the retroviral vector of claim 1, and as such, does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be packaged, as recited in claim 28.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 28 over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban.

Accordingly, appellant respectfully submits that the rejection of claim 28 over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed.

D.6. Argument for dependent claims 20 and 21

The rejection of claims 20 and 21 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed.

Claims 20 and 21 depend from and further limit claim 28. Claims 20 and 21 essentially recite methods for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells by infecting the cells with recombinant retroviruses produced by the producer cell line of claim 28 (claim 20), wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters, and combinations thereof (claim 21).

Appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 20 and 21 for the reasons presented hereinabove with respect to claim 1 and claim 28. Particularly, the combination of Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, does not teach or suggest the retroviral vector of claim 1, and as such, does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be packaged, as recited in claims 20 and 21.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claims 20 and 21 over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban.

Accordingly, it is respectfully submitted that the rejection of claims 20 and 21 as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed.

D.7. Argument for independent claim 33

The rejection of claim 33 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, does not teach or suggest the subject matter of these claims.

Claim 33 essentially recites the retroviral vector of claim 1, wherein the heterologous promoter is a promoter from a cellular gene. Appellant respectfully submits that since the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, does not teach or suggest the retroviral vector of claim 1, the combination does not support an obviousness rejection of a retroviral vector of claim 1, wherein the heterologous promoter is a cellular promoter, as recited in claim 33.

Additionally, appellant respectfully submits that Mehigh appears to be relied in for its teaching of the whey acidic protein and MMTV promoters. However, appellant respectfully submits that Mehigh does not teach that these promoters are located in the

3' U3 region and control transcription of coding sequences present in the body of the vector after promoter conversion. With reference to Figure 3 of Mehigh, it is clear that the disclosure of Mehigh is limited to employing these promoters already operably linked to a coding sequence in the body of the vector.

Furthermore, appellant respectfully submits that there is no motivation to combine Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban and as proposed by the Patent Office for the reasons presented hereinabove. Summarily, appellant respectfully submits that Couture does not teach a vector with a 3' U3 deletion nor does it suggest the need for using a polylinker for cloning purposes, and Faustinella and Mee teach against deleting 3' U3 sequences and then introducing a promoter and/or regulatory sequences alone into the deletion because to do so would destroy the self-inactivation character of the vector disclosed in these references. Additionally, the disclosure of Mehigh is limited to employing these promoters already operably linked to a coding sequence in the body of the vector. Further, the disclosures of Miller and Panganiban are limited to vectors containing modifications of retroviral protein genes or packaging signals (Miller) and/or the identification of the location of the int locus. The vectors do not include 3' U3 deletions, heterologous promoters, and polylinkers located within the 3' LTR.

As such, appellant respectfully submits that the instant rejection is based on an impermissible hindsight reconstruction of the cited Couture, Faustinella, and Mee or Mehigh references as evidenced by Miller and Panganiban, and thus the Patent Office has not presented a *prima facie* case of obviousness of claim 33.

Accordingly, appellant respectfully submits that the rejection of claim 33 over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed.

D.8. Argument for dependent claims 34-36, 38, 39, 42, 49, 54, and 55

Claims 34-36, 38, 39, 42, 49, 54, and 55 depend from and further limit claim 33. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed for the reasons stated above with regard to claims 1 and 33.

Additionally, with respect to claim 39, appellant respectfully submits that the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, does not teach or suggest a retroviral vector wherein the marker or therapeutic gene that is present within the body of the vector is a member of the Markush group recited in claim 39 and for which expression is regulated by the promoter and/or regulatory elements cloned into the 3' U3 sequence only after promoter conversion. Rather, appellant respectfully submits that while Couture discloses a neo gene present within the body of the vector, it is operatively linked to an SV40 promoter in the vector.

Thus, the neo gene in the Couture vectors is constitutively expressed in any cell that the retroviral vector enters. This is unlike the neo gene recited in claim 39, which would only be expressed in those cells in which the promoter and/or regulator elements present in the 3' U3 region is active. Accordingly, appellant respectfully submits that the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and

Panganiban, does not teach or suggest the vectors of claim 39 for this additional reason.

D.9. Argument for independent claim 43

The rejection of claim 43 as unpatentable over Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, does not teach or suggest the subject matter of these claims.

Claim 43 essentially recites a retroviral vector kit comprising the retroviral vector of claim 33 and a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged. Appellant respectfully submits that since the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, does not teach or suggest the retroviral vector of claim 33, the combination does not support an obviousness rejection of a kit comprising the retroviral vector of claim 33, as recited in claim 43.

Furthermore, appellant respectfully submits that there is no motivation to combine Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban and as proposed by the Patent Office for the reasons presented hereinabove. Summarily, appellant respectfully submits that Couture does not teach a vector with a 3' U3 deletion nor does it suggest the need for using a polylinker for

cloning purposes, and Faustinella and Mee teach against deleting 3' U3 sequences and then introducing a promoter and/or regulatory sequences alone into the deletion because to do so would destroy the self-inactivation character of the vector disclosed in these references. Additionally, the disclosure of Mehigh is limited to employing these promoters already operably linked to a coding sequence in the body of the vector. Further, the disclosures of Miller and Panganiban are limited to vectors containing modifications of retroviral protein genes or packaging signals (Miller) and/or the identification of the location of the int locus. The vectors do not include 3' U3 deletions, heterologous promoters, and polylinkers located within the 3' LTR.

As such, appellant respectfully submits that the instant rejection is based on an impermissible hindsight reconstruction of the cited Couture, Faustinella, and Mee or Mehigh references as evidenced by Miller and Panganiban, and thus the Patent Office has not presented a *prima facie* case of obviousness of claim 43.

Accordingly, appellant respectfully submits that the rejection of claim 43 over Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed.

D.10. Argument for dependent claims 44-48

Claims 44-48 depend from and further limit claim 43. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed for the reasons stated above with regard to claims 1 and 43.

D.11. Argument for independent claim 51

The rejection of claim 51 as unpatentable over Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban does not teach or suggest the subject matter of these claims.

Claim 51 essentially recites a producer cell line comprising the retroviral vector of claim 33 and a DNA construct coding for proteins required for the retroviral vector to be packaged. Appellant respectfully submits that since the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, does not teach or suggest the retroviral vector of claim 33, the combination does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 33, as recited in claim 51.

Furthermore, appellant respectfully submits that there is no motivation to combine Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban as proposed by the Patent Office for the reasons presented hereinabove. Summarily, appellant respectfully submits that Couture does not teach a vector with a 3' U3 deletion nor does it suggest the need for using a polylinker for cloning purposes, and Faustinella and Mee teach against deleting 3' U3 sequences and then introducing a promoter and/or regulatory sequences alone into the deletion because to do so would

destroy the self-inactivation character of the vector disclosed in these references. Additionally, the disclosure of Mehigh is limited to employing these promoters already operably linked to a coding sequence in the body of the vector. Further, the disclosures of Miller and Panganiban are limited to vectors containing modifications of retroviral protein genes or packaging signals (Miller) and/or the identification of the location of the int locus. The vectors do not include 3' U3 deletions, heterologous promoters, and polylinkers located within the 3' LTR.

As such, appellant respectfully submits that the instant rejection is based on an impermissible hindsight reconstruction of the cited Couture, Faustinella, and Mee or Mehigh references as evidenced by Miller and Panganiban, and thus the Patent Office has not presented a *prima facie* case of obviousness of claim 51.

Accordingly, appellant respectfully submits that the rejection of claim 51 over Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, should be reversed.

D.12. Argument for dependent claims 52 and 53

Claims 52 and 53 depend from and further limit claim 51. Claims 52 and 53 essentially recite methods for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells by infecting the cells with recombinant retroviruses produced by the producer cell line of claim 51 (claim 52), wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters, and combinations thereof (claim 53).

Appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claims 52 and 53 for the reasons presented hereinabove with respect to claim 33 and claim 51. Particularly, the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, does not teach or suggest the retroviral vector of claim 33, or the producer cell line comprising the retroviral vector of claim 33 and a DNA construct coding for proteins required for the retroviral vector to be packaged as recited in claim 51. As a result, appellant respectfully submits that the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban, does not support an obviousness rejection of claims to methods of using a retroviral vector of claim 33 produced by the producer cell line of claim 51 as recited in claims 52 and 53.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that since there is no motivation to combine the Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban references as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claims 52 and 53 over Couture, Faustinella, and Mee or Mehigh as evidenced by Miller and Panganiban.

Accordingly, it is respectfully submitted that the rejection of claims 52 and 53 as being unpatentable over Couture and Faustinella and further in view of Mee or Mehigh as evidenced by Miller and Panganiban should be reversed.

E. Rejection of claims 1, 10, 33, 37, 56, and 60 under 35 U.S.C. § 103(a) as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Price

E.1. Argument for independent claim 1

The rejection of claim 1 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Price, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture and Faustinella, and further in view of Mee or Mehigh as further evidenced by Price, does not teach or suggest the subject matter of these claims.

Appellant respectfully submits that even assuming *arguendo* that the Patent Office's characterization of the Price reference is correct, this reference does not cure the deficiencies discussed hereinabove for the combination of Couture and Faustinella in view of Mee or Mehigh. The BAG vector of Price has a complete 3' U3 (*see* Figure 1 of Price), and is similar to Couture in that expression of the gene of interest is directed by a fully functional LTR. This is in contrast to the presently claimed vectors, which subsequent to promoter conversion do not contain a complete 3' LTR. Thus, appellant respectfully submits that Price does not cure the deficiencies noted hereinabove with respect to the Couture and Faustinella references in view of Mee or Mehigh, and as

such, Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Price does not support a rejection of claim 1 under § 103.

Furthermore, appellant respectfully submits that there is no motivation to combine Couture and Faustinella with Mee or Mehigh based on the disclosure of Price as proposed by the Patent Office for the reasons presented hereinabove. Summarily, appellant respectfully submits that Couture does not teach a vector with a 3' U3 deletion nor does it suggest the need for using a polylinker for cloning purposes, and Faustinella and Mee teach against deleting 3' U3 sequences and then introducing a promoter and/or regulatory sequences alone into the deletion because to do so would destroy the self-inactivation character of the vectors disclosed therein. Additionally, it is clear that the disclosure of Mehigh is limited to employing these promoters already operably linked to a coding sequence in the body of the vector. Further, the disclosure of Price appears to be limited to vectors having a complete 3' U3 (*see* Figure 1 of Price), and is similar to Couture in that expression of the gene of interest is directed by a fully functional LTR. Appellant therefore respectfully submits that the proposed combination does not provide the motivation to create a retroviral vector that is characterized by a partially deleted 3' U3 region, and thus does not support the instant rejection for this additional reason.

Accordingly, appellant respectfully requests that the obviousness rejection of claim 1 over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Price, be reversed.

E.2. Argument for dependent claim 10

Claim 10 depends from and further limits claim 1. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Price, should be reversed for the reasons stated above with regard to claim 1.

E.3. Argument for independent claim 33

The rejection of claim 33 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Price, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Price, does not teach or suggest the subject matter of these claims.

Claim 33 essentially recites the retroviral vector of claim 1, wherein the heterologous promoter is a promoter from a cellular gene. Appellant respectfully submits that since Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Price, does not teach or suggest the retroviral vector of claim 1, the combination does not support an obviousness rejection of a retroviral vector of claim 1, wherein the heterologous promoter is a cellular promoter, as recited in claim 33.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee or Mehigh references as evidenced by Price as proposed by the Patent Office. As such,

the Patent Office has not presented a *prima facie* case of obviousness of claim 33 over Couture, Faustinella, and Mee or Mehigh as evidenced by Price.

Accordingly, appellant respectfully submits that the rejection of claim 33 over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Price, should be reversed.

E.4. Argument for dependent claim 37

Claim 37 depends from and further limits claim 33. Accordingly, it is respectfully submitted that the rejection of this claim as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Price, should be reversed for the reasons stated above with regard to claims 1 and 33.

E.5. Argument for independent claim 56

The rejection of claim 56 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Price, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Price, does not teach or suggest the subject matter of these claims.

Claim 56 essentially recites the retroviral vector of claim 1, wherein the heterologous promoter is a heterologous retroviral promoter. Appellant respectfully submits that since Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Price, does not teach or suggest the retroviral vector of claim 1, the

combination does not support an obviousness rejection of a retroviral vector of claim 1, wherein the heterologous promoter is a heterologous retroviral promoter, as recited in claim 56.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee or Mehigh references as evidenced by Price as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 56 over Couture, Faustinella, and Mee or Mehigh as evidenced by Price.

Accordingly, appellant respectfully submits that the rejection of claim 56 over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Price, should be reversed.

E.6. Argument for dependent claim 60

Claim 60 depends from and further limit claims 56. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Price, should be reversed for the reasons stated above with regard to claims 1 and 56.

F. Rejection of claims 17, 20, 21, 26, 28, 43, 50-53, 66, and 73-76 under 35 U.S.C. § 103(a) as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh, as further evidenced by Longmore and Kay

F.1. Argument for independent claim 17

The rejection of claim 17 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture and Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, does not teach or suggest the subject matter of these claims.

Appellant respectfully submits that even assuming *arguendo* that the Patent Office's characterization of the Longmore and Kay references is correct, these references do not cure the deficiencies discussed hereinabove for the combination of Couture and Faustinella. More particularly, the spleen focus-forming virus of Longmore and the modified LNCX vector of Kay both have a complete 3' U3. This is in contrast to the presently claimed vectors, which subsequent to promoter conversion direct transcription of the gene of interest through a promoter lacking a complete U3 sequence. As a result, Longmore and Kay do not cure the deficiencies of the Couture and Faustinella references discussed herein.

Furthermore, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee or Mehigh references as evidenced by Longmore and Kay as proposed by the Patent Office for the reasons presented hereinabove. Summarily, appellant respectfully submits that Couture does not teach a vector with a 3' U3 deletion nor does it suggest the need for using a polylinker for cloning purposes, and Faustinella and Mee teach against deleting 3' U3 sequences and then introducing a promoter and/or regulatory sequences alone into the deletion because to do so would destroy the self-inactivation character of the vectors disclosed therein. Additionally, it is clear that the disclosure of Mehigh is limited to employing these promoters already operably linked to a coding sequence in the body of the vector. Additionally, the spleen focus-forming virus of Longmore and the modified LNCX vector of Kay both have a complete 3' U3. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 17 over Couture, Faustinella, and Mee or Mehigh as evidenced by Longmore and Kay.

Accordingly, appellant respectfully requests that the obviousness rejection of claim 17 over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, be reversed.

F.2. Argument for dependent claim 26

Claim 26 depends from and further limits claim 17. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed for the reasons stated above with regard to claims 1 and 17.

F.3. Argument for independent claim 28

The rejection of claim 28 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, does not teach or suggest the subject matter of these claims.

Claim 28 essentially recites a producer cell line comprising the retroviral vector of claim 1 and a DNA construct coding for proteins required for the retroviral vector to be packaged. Appellant respectfully submits that since Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, does not teach or suggest the retroviral vector of claim 1, the combination does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 1, as recited in claim 28.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee or Mehigh references as evidenced by Longmore and Kay as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 28 over Couture, Faustinella, and Mee or Mehigh as evidenced by Longmore and Kay.

Accordingly, appellant respectfully submits that the rejection of claim 28 over Couture in view of Faustinella, and further in view of Mee or Mehigh, as further evidenced by Longmore and Kay, should be reversed.

F.4. Argument for independent claim 43

The rejection of claim 43 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, does not teach or suggest the subject matter of these claims.

Claim 43 essentially recites a retroviral vector kit comprising the retroviral vector of claim 33 and a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged. Appellant respectfully submits that since Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, does not teach or suggest the retroviral vector of claim 33, the combination does not support an obviousness rejection of a kit comprising the retroviral vector of claim 33, as recited in claim 43.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee or

Mehigh references as evidenced by Longmore and Kay as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 43 over Couture, Faustinella, and Mee or Mehigh as evidenced by Longmore and Kay.

Accordingly, appellant respectfully submits that the rejection of claim 43 over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed.

F.5. Argument for dependent claim 50

Claim 50 depends from and further limits claim 43. Accordingly, it is respectfully submitted that the rejection of these claims as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed for the reasons stated above with regard to claims 1 and 43.

F.6. Argument for independent claim 51

The rejection of claim 51 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, does not teach or suggest the subject matter of these claims.

Claim 51 essentially recites a producer cell line comprising the retroviral vector of claim 33 and a DNA construct coding for proteins required for the retroviral vector to be packaged. Appellant respectfully submits that since Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, does not teach or suggest the retroviral vector of claim 33, the combination does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 33, as recited in claim 51.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee or Mehigh references as evidenced by Longmore and Kay as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 51 over Couture, Faustinella, and Mee or Mehigh as evidenced by Longmore and Kay.

Accordingly, appellant respectfully submits that the rejection of claim 51 over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed.

F.7. Argument for dependent claims 52 and 53

Claims 52 and 53 depend from and further limit claim 51. Claims 52 and 53 essentially recite methods for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells by infecting the cells with recombinant retroviruses produced by the producer cell line of claim 51 (claim 52), wherein the nucleotide sequences are selected from the group consisting of genes or

parts of genes encoding for proteins, regulatory sequences and promoters, and combinations thereof (claim 53).

Appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claims 52 and 53 for the reasons presented hereinabove with respect to claim 33 and claim 51. Particularly, the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Longmore and Kay, does not teach or suggest the retroviral vector of claim 33, or the producer cell line comprising the retroviral vector of claim 33 and a DNA construct coding for proteins required for the retroviral vector to be packaged as recited in claim 51. As a result, appellant respectfully submits that the combination of Couture, Faustinella, and Mee or Mehigh as evidenced by Longmore and Kay, does not support an obviousness rejection of claims to methods of using a retroviral vector of claim 33 produced by the producer cell line of claim 51 as recited in claims 52 and 53.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee or Mehigh references as evidenced by Longmore and Kay as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claims 52 and 53 over Couture, Faustinella, and Mee or Mehigh as evidenced by Longmore and Kay.

Accordingly, it is respectfully submitted that the rejection of claims 52 and 53 as being unpatentable over Couture, Faustinella, and Mee or Mehigh as evidenced by Longmore and Kay should be reversed.

F.8. Argument for independent claim 66

The rejection of claim 66 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh, as further evidenced by Longmore and Kay, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, does not teach or suggest the subject matter of these claims.

Claim 66 essentially recites a retroviral vector kit comprising the retroviral vector of claim 56 and a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged. Appellant respectfully submits that since Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, does not teach or suggest the retroviral vector of claim 56, the combination does not support an obviousness rejection of a kit comprising the retroviral vector of claim 56, as recited in claim 66.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee or Mehigh references as evidenced by Longmore and Kay as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness

of claim 66 over Couture, Faustinella, and Mee or Mehigh as evidenced by Longmore and Kay.

Accordingly, appellant respectfully submits that the rejection of claim 66 over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed.

F.9. Argument for dependent claim 73

Claim 73 depends from and further limits claim 66. Accordingly, it is respectfully submitted that the rejection of this claim as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed for the reasons stated above with regard to claims 1 and 66.

F.10. Argument for independent claim 74

The rejection of claim 74 as unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed because it is only by using impermissible hindsight reconstruction that the cited references can be combined in an attempt to arrive at the presently claimed subject matter. Additionally, appellant respectfully submits that even if the cited references are combined, the references must be considered in their entireties, and when this is done, it is clear that Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, does not teach or suggest the subject matter of these claims.

Claim 74 essentially recites a producer cell line comprising the retroviral vector of claim 56 and a DNA construct coding for proteins required for the retroviral vector to be

packaged. Appellant respectfully submits that since Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, does not teach or suggest the retroviral vector of claim 56, the combination does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 56.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee or Mehigh references as evidenced by Longmore and Kay as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claim 74 over Couture, Faustinella, and Mee or Mehigh as evidenced by Longmore and Kay.

Accordingly, appellant respectfully submits that the rejection of claim 74 over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed.

F.11. Argument for dependent claims 75 and 76

Claims 75 and 76 depend from and further limit claim 74. Claims 75 and 76 essentially recite methods for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells by infecting the cells with recombinant retroviruses produced by the producer cell line of claim 74 (claim 75), wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters, and combinations thereof (claim 76).

Appellant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claims 75 and 76 for the reasons presented hereinabove

with respect to claim 56 and claim 74. Particularly, the combination of Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, does not teach or suggest the retroviral vector of claim 56, and as such, does not support an obviousness rejection of a producer cell line comprising the retroviral vector of claim 56 and a DNA construct coding for proteins required for the retroviral vector to be packaged.

Furthermore, for the reasons set forth herein above, appellant respectfully submits that there is no motivation to combine the Couture, Faustinella, and Mee or Mehigh references as evidenced by Longmore and Kay as proposed by the Patent Office. As such, the Patent Office has not presented a *prima facie* case of obviousness of claims 75 and 76 over Couture, Faustinella, and Mee or Mehigh as evidenced by Longmore and Kay.

Accordingly, it is respectfully submitted that the rejection of claims 75 and 76 as being unpatentable over Couture in view of Faustinella, and further in view of Mee or Mehigh as further evidenced by Longmore and Kay, should be reversed.

G. Conclusions

All of the rejections under 35 U.S.C. § 103(a) of the pending claims are based at least in part on the combination of Couture and Faustinella, which is asserts to suggest a retroviral vector comprising a deletion in the 3' U3 region, into which a heterologous promoter and/or regulatory sequence can be cloned with the aid of a polylinker. However, appellant respectfully submits that the Patent Office has not met its burden in establishing a *prima facie* case of obviousness of the claims at issue based upon this

combination. The *prima facie* case fails because the cited references do not suggest retroviral vectors containing an incomplete 3' U3 region and a heterologous promoter that upon promoter conversion becomes operatively linked to a gene of interest to which it was not operatively linked prior to the promoter conversion event as recited in claim 1.

More particularly, Couture teaches retroviral vectors containing complete, chimeric 3' LTRs, and while Faustinella teaches an insertion of a polylinker into a 3' U3 deletion, the polylinker is used in Faustinella to clone promoter/coding sequence pairs into the 3' LTR. Appellant respectfully submits that there is no suggestion or motivation found in the combination of Couture and Faustinella to produce retroviral vectors by creating a 3' U3 deletion and cloning heterologous (*e.g.*, cellular or retroviral) promoters and/or regulatory sequences alone into a 3' U3 deletion. Appellant respectfully submits that it is only with hindsight vision that the Patent Office was able to combine the references as presented in the Final Official Action.

Furthermore, appellant respectfully submits that the Patent Office has articulated no motivation for combining the references as proposed in the Final Official Action. Appellant further respectfully submits that no such motivation can be found, as Couture does not teach a vector with a 3' U3 deletion nor does it suggest the need for using a polylinker for cloning purposes, and Faustinella teaches against deleting 3' U3 sequences and then introducing a promoter and/or regulatory sequences alone into the deletion because to do so would destroy the self-inactivation character of the vector that the U3 deletion was designed to create. Appellant respectfully submits that none of the other cited references, including Mee, Mehigh, Miller, Panganiban, Price, Longmore, or Kay, either alone or in combination, provide a sufficient motivation.

Accordingly, appellant respectfully submits that the Patent Office has not established a *prima facie* case of obviousness of any of claims 1, 5, 7, 9-26, 28, 29, and 31-78 over Couture in view of Faustinella, and further in view of Mee or Mehigh as evidenced by Miller and Panganiban, Price, or Longmore and Kay.

Accordingly, appellant respectfully requests that the aforementioned rejections of claims 1, 5, 7, 9-26, 28, 29, and 31-78 under 35 U.S.C. § 103(a) over the cited combinations be reversed, and that the claims be allowed at this time.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this paper to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON & TAYLOR, P.A.

Date: 20 Dec. 2005 By: _____

Arles A. Taylor, Jr.
Registration No. 39,395

1406/194 AAT/CPP/acy

Customer No: 25297

VIII. Claims Appendix

1. A retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

(a) a 5' long terminal repeat region of the structure U3-R-U5;

(b) one or more coding sequences, said sequences being inserted into the body of the vector; and

(c) a 3' long terminal repeat region comprising a partially deleted U3 region into which a polylinker sequence containing a heterologous promoter has been inserted,

wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous promoter and said heterologous promoter regulating expression of said one or more coding sequences in said target cell.

5. The retroviral vector according to Claim 1, wherein said retroviral vector further comprises a regulatory element other than a promoter.

7. The retroviral vector according to Claim 1, wherein said heterologous promoter is selected from the group consisting of: a Whey Acidic Protein specific promoter, a Mouse Mammary Tumor Virus specific promoter, β-lactoglobulin and casein specific promoters, a pancreas specific promoter, a lymphocyte specific promoter, a Mouse Mammary Tumor Virus specific promoter conferring responsiveness to glucocorticoid hormones or directing expression to the mammary gland, and combinations thereof.

9. The retroviral vector according to Claim 1, wherein each long terminal repeat region is derived from a retrovirus selected from the group consisting of Murine Leukaemia Virus, Mouse Mammary Tumor Virus, Murine Sarcoma Virus, Simian Immunodeficiency Virus, Human Immunodeficiency Virus, Human T Cell Leukaemia Virus, Feline Immunodeficiency Virus, Feline Leukaemia Virus, Bovine Leukaemia Virus, Mason-Pfizer-Monkey Virus, and combinations thereof.

10. The retroviral vector according to Claim 1, wherein said retroviral vector is derived from a BAG vector.

11. The retroviral vector according to Claim 1, wherein the coding sequences are selected from the group consisting of marker genes, therapeutic genes, antiviral genes, antitumor genes, cytokine genes and combinations thereof.

12. The retroviral vector according to Claim 11, wherein said marker or therapeutic genes are selected from the group consisting of β-galactosidase gene, neomycin gene, Herpes Simplex Virus thymidine kinase gene, puromycin gene, cytosine deaminase gene, hygromycin gene, secreted alkaline phosphatase gene, guanine phosphoribosyl transferase (gpt) gene, alcohol dehydrogenase gene, hypoxanthine phosphoribosyl transferase (HPRT) gene and combinations thereof.

13. The retroviral vector according to Claim 1, wherein at least one of said coding sequences is a retroviral coding sequence that is an altered or at least partially deleted retroviral gene.

14. The retroviral vector according to Claim 1, wherein retroviral sequences involved in integration of retroviruses are altered or at least partially deleted.

15. The retroviral vector according to Claim 1, wherein said vector comprises one or more sequences homologous to one or more cellular sequences or a part thereof.

16. The retroviral vector according to Claim 5, wherein said regulatory element is regulatable by transacting molecules.

17. A retroviral vector kit comprising:

(a) a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

(i) a 5' long terminal repeat region of the structure U3-R-U5;

(ii) one or more coding sequences, said sequences being inserted into the body of the vector; and

(iii) a 3' long terminal repeat region comprising a partially deleted U3 region into which a polylinker sequence containing a heterologous promoter has been inserted, wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous promoter and said heterologous promoter regulating expression of said one or more coding sequences in said target cell; and

(b) a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged.

18. The retroviral vector system according to Claim 17 wherein the packaging cell line harbors retroviral or recombinant retroviral constructs coding for those retroviral proteins which are not encoded in said retroviral vector.

19. The retroviral vector system according to Claim 17 wherein the packaging cell line is selected from the group consisting of psi-2, psi-Crypt, psi-AM, GP+E-86, PA317, and GP+envAM-12.

20. A method for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells, said method comprising infecting the cells with recombinant retroviruses produced by the producer cell line of Claim 28.

21. The method according to Claim 20, wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters and combinations thereof.

22. Recombinant retroviral particle obtained by transfecting a packaging cell line of a retroviral vector kit according to Claim 17 with the retroviral vector according to Claim 17, and culturing the cells under suitable conditions.

23. A retroviral provirus produced by infection of target cells with a recombinant retroviral particle according to Claim 22 whereby the heterologous DNA fragment in the 3' long terminal repeat becomes duplicated during the process of reverse transcription in the target cell and appears in the 5' long terminal repeat as well as in the 3' long terminal repeat of the resulting provirus.

24. mRNA of the retroviral provirus according to Claim 23.

25. RNA of a retroviral vector according to Claim 1.

26. Pharmaceutical composition containing a therapeutically effective amount of a recombinant retroviral particle according to Claim 22.

28. A producer cell line producing a retroviral particle, the producer cell comprising a retroviral vector and a DNA construct coding for proteins required for the retroviral vector to be packaged, said retroviral vector comprising in 5' to 3' order,

(a) a 5' long terminal repeat region of the structure U3-R-U5;

(b) one or more coding sequences, said sequences being inserted into the body of the vector; and

(c) a 3' long terminal repeat region comprising a partially deleted U3 region into which a polylinker sequence containing a heterologous promoter has been inserted,

wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous promoter and said heterologous promoter regulating expression of said one or more coding sequences in said target cell.

29. A recombinant retroviral particle comprising the retroviral vector according to Claim 1.

31. The retroviral vector according to Claim 1, wherein said promoter is target cell specific in its expression.

32. The retroviral vector according to Claim 5, wherein said regulatory element is target specific in its expression.

33. A retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

(a) a 5' long terminal repeat region of the structure U3-R-U5;

(b) one or more coding sequences, said sequences being inserted into the body of the vector; and

(c) a 3' long terminal repeat region comprising a partially deleted U3 region into which a polylinker sequence containing a promoter from a cellular gene has been inserted,

wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said promoter from a cellular gene, resulting in said one or more coding sequences becoming operatively linked to said promoter from a cellular gene and said promoter from a cellular gene regulating expression of said one or more coding sequences in said target cell.

34. The retroviral vector according to Claim 33, wherein said vector further comprises a regulatory element other than a promoter.

35. The retroviral vector according to Claim 33, wherein said promoter is selected from the group consisting of: a Whey Acidic Protein promoter, β-lactoglobulin and casein specific promoters, a pancreas specific promoter, lymphocyte specific promoters, and combinations thereof.

36. The retroviral vector according to Claim 33, wherein each long terminal repeat region is derived from a retrovirus selected from the group consisting of Murine Leukaemia Virus, Mouse Mammary Tumor Virus, Murine Sarcoma Virus, Simian Immunodeficiency Virus, Human Immunodeficiency Virus, Human T Cell Leukaemia

Virus, Feline Immunodeficiency Virus, Feline Leukaemia Virus, Bovine Leukaemia Virus, Mason-Pfizer-Monkey Virus, and combinations thereof.

37. The retroviral vector according to Claim 33, wherein said retroviral vector is derived from a BAG vector.

38. The retroviral vector according to Claim 33, wherein the coding sequences are selected from the group consisting of marker genes, therapeutic genes, antiviral genes, antitumor genes, cytokine genes and combinations thereof.

39. The retroviral vector according to Claim 38, wherein said marker or therapeutic genes are selected from the group consisting of β-galactosidase gene, neomycin gene, Herpes Simplex Virus thymidine kinase gene, puromycin gene, cytosinedeaminase gene, hygromycin gene, secreted alkaline phosphatase gene, guaninephosphoribosyl transferase (gpt) gene, alcohol dehydrogenase gene, hypoxanthine phosphoribosyl transferase (HPRT) gene and combinations thereof.

40. The retroviral vector according to Claim 33, wherein at least one of said coding sequences is a retroviral coding sequence that is an altered or at least-partially deleted retroviral gene.

41. The retroviral vector according to Claim 33, wherein retroviral sequences involved in integration of retroviruses are altered or at least partially deleted.

42. The retroviral vector according to Claim 33, wherein said promoter is regulatable by transacting molecules.

43. A retroviral vector kit comprising:

(a) a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

(i) a 5' long terminal repeat region of the structure U3-R-U5;

(ii) one or more coding sequences, said sequences being inserted into the body of the vector; and

(iii) a 3' long terminal repeat region comprising a partially deleted U3 region into which a polylinker sequence containing a promoter from a cellular gene has been inserted, wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said promoter from a cellular gene, resulting in said one or more coding sequences becoming operatively linked to said promoter from a cellular gene and said promoter from a cellular gene regulating expression of said one or more coding sequences in said target cell; and

(b) a packaging cell line comprising at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged.

44. The retroviral vector system according to Claim 43 wherein the packaging cell line harbors retroviral or recombinant retroviral constructs coding for those retroviral proteins which are not encoded in said retroviral vector.

45. The retroviral vector system according to Claim 44 wherein the packaging cell line is selected from the group consisting of psi-2, psi-Crypt, psi-AM, GP+E-86, PA317, and GP+envAM-12.

46. Recombinant retroviral particle obtained by transfecting a packaging cell line of a retroviral vector kit according to Claim 43 with the retroviral vector according to Claim 43, and culturing the cells under suitable conditions.

47. A retroviral provirus produced by infection of target cells with a recombinant retroviral particle according to Claim 46 whereby the promoter in the 3' long terminal repeat becomes duplicated during the process of reverse transcription in the target cell and appears in the 5' long terminal repeat as well as in the 3' long terminal repeat of the resulting provirus.

48. mRNA of the retroviral provirus according to Claim 47.

49. RNA of a retroviral vector according to Claim 33.

50. Pharmaceutical composition containing a therapeutically effective amount of a recombinant retroviral particle according to Claim 46.

51. A producer cell line producing a retroviral particle, the producer cell comprising a retroviral vector and a DNA construct coding for proteins required for the retroviral vector to be packaged, said retroviral vector comprising in 5' to 3' order,

(a) a 5' long terminal repeat region of the structure U3-R-U5;

(b) one or more coding sequences, said sequences being inserted into the body of the vector; and

(c) a 3' long terminal repeat region comprising a partially deleted U3 region into which a polylinker sequence containing a promoter from a cellular gene has been inserted,

wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said promoter from a cellular

gene, resulting in said one or more coding sequences becoming operatively linked to said promoter from a cellular gene and said promoter from a cellular gene regulating expression of said one or more coding sequences in said target cell.

52. A method for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells, said method comprising infecting the cells with recombinant retroviruses produced by the producer cell line of Claim 51.

53. The method according to Claim 52, wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters and combinations thereof.

54. A recombinant retroviral particle comprising the retroviral vector according to Claim 33.

55. The retroviral vector according to Claim 33, wherein said promoter is target cell specific in its expression.

56. A retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

(a) a 5' long terminal repeat region of the structure U3-R-U5;

(b) one or more coding sequences, said sequences being inserted into the body of the vector; and

(c) a 3' long terminal repeat region comprising a partially deleted U3 region into which a polylinker sequence containing a heterologous retroviral promoter has been inserted,

wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous retroviral

promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous retroviral promoter and said heterologous retroviral promoter regulating expression of said one or more coding sequences in said target cell.

57. The retroviral vector according to Claim 56, wherein said vector further comprises a regulatory element other than a promoter.

58. The retroviral vector according to Claim 56, wherein said promoter is selected from the group consisting of a Mouse mammary Tumor specific promoter, a Mouse Mammary Tumor Virus specific promoter conferring responsiveness to glucocorticoid hormones or directing expression to the mammary gland, and combinations thereof.

59. The retroviral vector according to Claim 56, wherein each long terminal repeat region is derived from a retrovirus selected from the group consisting of Murine Leukaemia Virus, Mouse Mammary Tumor Virus, Murine Sarcoma Virus, Simian Immunodeficiency Virus, Human Immunodeficiency Virus, Human T Cell Leukaemia Virus, Feline Immunodeficiency Virus, Feline Leukaemia Virus, Bovine Leukaemia Virus, Mason-Pfizer-Monkey Virus, and combinations thereof.

60. The retroviral vector according to Claim 56, wherein said retroviral vector is derived from a BAG vector.

61. The retroviral vector according to Claim 56, wherein the coding sequences are selected from the group consisting of marker genes, therapeutic genes, antiviral genes, antitumor genes, cytokine genes and combinations thereof.

62. The retroviral vector according to Claim 61, wherein said marker or therapeutic genes are selected from the group consisting of β-galactosidase gene,

neomycin gene, Herpes Simplex Virus thymidine kinase gene, puromycin gene, cytosine deaminase gene, hygromycin gene, secreted alkaline phosphatase gene, guanine phosphoribosyl transferase (gpt) gene, alcohol dehydrogenase gene, hypoxanthine phosphoribosyl transferase (HPRT) gene and combinations thereof.

63. The retroviral vector according to Claim 56, wherein at least one of said coding sequences is a retroviral coding sequence that is an altered or at least partially deleted retroviral gene.

64. The retroviral vector according to Claim 56, wherein retrovira lsequences involved in integration of retroviruses are altered or at least partially deleted.

65. The retroviral vector according to Claim 56, wherein said promoter is regulatable by transacting molecules.

66. A retroviral vector kit comprising:

(a) a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

(i) a 5' long terminal repeat region of the structure U3-R-U5;

(ii) one or more coding sequences, said sequences being inserted into the body of the vector; and

(iii) a 3' long terminal repeat region comprising a partially deleted U3 region into which a polylinker sequence containing a heterologous retroviral promoter has been inserted, wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous retroviral promoter, resulting in said one or more coding sequences

becoming operatively linked to said heterologous retroviral promoter and said heterologous retroviral promoter regulating expression of said one or more coding sequences in said target cell; and

(b) a packaging cell line harboring at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged.

67. The retroviral vector system according to Claim 66 wherein the packaging cell line harbors retroviral or recombinant retroviral constructs coding for those retroviral proteins which are not encoded in said retroviral vector.

68. The retroviral vector system according to Claim 66 wherein the packaging cell line is selected from the group consisting of psi-2, psi-Crypt, psi-AM, GP+E-86, PA317, and GP+envAM-12.

69. Recombinant retroviral particle obtained by transfecting a packaging cell line of a retroviral vector kit according to Claim 66 with the retroviral vector according to Claim 66, and culturing the cells under suitable conditions.

70. A retroviral provirus produced by infection of target cells with a recombinant retroviral particle according to Claim 69 whereby the promoter in the 3' long terminal repeat becomes duplicated during the process of reverse transcription in the target cell and appears in the 5' long terminal repeat as well as in the 3' long terminal repeat of the resulting provirus.

71. mRNA of the retroviral provirus according to Claim 70.

72. RNA of a retroviral vector according to Claim 56.

73. Pharmaceutical composition containing a therapeutically effective amount of a recombinant retroviral particle according to Claim 69.

74. A producer cell line producing a retroviral particle, the producer cell comprising a retroviral vector and a DNA construct coding for proteins required for the retroviral vector to be packaged, said retroviral vector comprising in 5' to 3' order,

(a) a 5' long terminal repeat region of the structure U3-R-U5;

(b) one or more coding sequences, said sequences being inserted into the body of the vector; and

(c) a 3' long terminal repeat region comprising a partially deleted U3 region into which a polylinker sequence containing a heterologous retroviral promoter has been inserted,

wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous retroviral promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous retroviral promoter and said heterologous retroviral promoter regulating expression of said one or more coding sequences in said target cell.

75. A method for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells, said method comprising infecting the cells with recombinant retroviruses produced by the producer cell line of Claim 74.

76. The method according to Claim 75, wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters and combinations thereof.

77. A recombinant retroviral particle comprising the retroviral vector according to Claim 56.

78. The retroviral vector according to Claim 56, wherein said promoter is target cell specific in its expression.

IX. Evidence Appendix

IX.1. Declaration of Christine Leib-Moesch Pursuant to 37 C.F.R. § 1.132

Applicant submitted a Declaration of Christine Leib-Moesch Pursuant to 37 C.F.R. § 1.132 on April 18, 2005. In an Advisory Action dated May 26, 2005, the Patent Office indicated that the Declaration had been entered into the record. A true and accurate copy of the Rule 132 Declaration is attached hereto.

I hereby certify that this paper is being facsimile transmitted to the United States Patent and Trademark Office on the date shown below.

Christi Butner
Christi Butner
Date of Signature: April 18, 2005

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gunzburg and Saller

Group Art Unit: 1631

Serial No.: 08/808,827

Examiner: Brusca, John S.

Filed: February 28, 1997

Docket No.: 1406/194

Confirmation No.: 6837

For: NON SELF-INACTIVATING, EXPRESSION TARGETED RETROVIRAL VECTORS

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DECLARATION OF CHRISTINE LEIB-MOESCH
PURSUANT TO 37 C.F.R. §§1.132

Commissioner of Patents
Washington, D.C. 20231

Sir:

1. My name is Christine Leib-Moesch, and I am currently research project leader at the GSF-Forschungszentrum fuer Umwelt und Gesundheit GmbH, assignee for the subject U.S. Patent Application Serial No. 08/808,827.

2. A true and accurate copy of my *curriculum vitae*, which evidences my expertise and credentials, is attached herewith and labeled **Exhibit A**.

3. I have had an opportunity to review pending claims 1, 5, 7, 9-26, 28, 29, and 31-78 in the subject above captioned U.S. Patent Application Serial No. 08/808,827.

4. I have also reviewed the following documents: the Final Official Action issued October 24, 2004 on the above captioned U.S. Patent Application Serial No. 08/808,827 by the U.S. Patent and Trademark Office; Couture *et al.* (5 *Human Gene*

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Therapy 667-677, 1994; hereinafter "Couture"); and Faustinella *et al.* (5 *Human Gene Therapy* 307-312, 1994; hereinafter "Faustinella") cited in the Official Action.

5. Couture describes retroviral vectors characterized by substitutions of portions of the 3' U3 regions with corresponding regions of 5 related murine retroviruses in order to create retroviral vectors with complete, chimeric 3' LTRs that display different tissue tropisms based on the presence of regulatory elements present within the U3 regions of the chimeric 3' LTRs. The replacement strategies disclosed in Couture produce complete chimeric LTRs "based on the substitution of the MoMLV U3 region with the U3 region from the murine retroviral isolates SL3-3, AKV, Xeno, HaMSV, and MPSV" (Couture at page 669). This was accomplished by employing conserved restriction sites present in the 3' LTRs of these retroviruses. As such, the vectors disclosed by Couture were specifically designed to have complete U3 regions.

6. There is no disclosure in Couture of any retroviral vector in which the U3 region of the 3' LTR contains a deletion. Rather, Couture teaches producing complete, although chimeric, 3' LTRs by "swapping" corresponding regions of the 3' U3 sequences of five related retroviruses into the vector.

7. Faustinella describes a MoMLV-based vector characterized by a partial deletion of the 3' U3 region into which a polylinker has been inserted. The strategy described in Faustinella is used to create self-inactivating vectors by deletion of the promoter/enhancer sequences present within the 3' LTR. The polylinkers were then added to facilitate the cloning of a promoter operatively linked to a coding sequence. Given that the purpose of the Faustinella strategy was to create self-inactivating vectors (SIN vectors), if the 3' LTR polylinker is to be used as a cloning site for a promoter, that promoter must be operatively linked to a gene of interest, because only when the inserted promoter is operatively linked to a gene of interest is a self-inactivating vector produced. Thus, Faustinella discloses two main strategies: (a) the deletion of regulatory sequences from the 3' U3 to create a SIN vector, which requires that the 3' U3 remain without regulatory sequences; and (b) the use of a polylinker to clone promoter/coding sequence pairs into the 3' U3 deletion, because if

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a promoter is cloned into the polylinker, then the SIN character of the vector is destroyed unless a coding sequence is operatively linked to this promoter.

8. There is no disclosure in Faustinella of any retroviral vector in which the U3 region of the 3' LTR contains a deletion and a heterologous promoter without there also being present a coding sequence operatively linked to the heterologous promoter in the 3' U3.

9. The claimed subject matter of the subject U.S. Patent Application Serial No. 08/808,827 relates to retroviral vectors that are characterized by the complete or partial deletion of the 3' U3 region and the replacement of part or all of the 3' U3 region with heterologous promoters and/or regulatory elements, which are then used to regulate expression of coding sequences that are present within the body of the vectors (*i.e.* are not operatively linked to the promoters and/or regulatory sequences in the vectors). Upon infection of a target cell, these heterologous promoters and/or regulatory elements become operatively linked to one or more coding sequences present within the body of the vector. As a result, the coding sequences present within the body of the vector, which can encode therapeutic polypeptides such as antiviral genes, antitumor genes, cytokine genes and combinations thereof, are expressed in those tissues and cell types in which the heterologous promoters and/or regulatory elements are active.

10. The claimed subject matter of the subject U.S. Patent Application Serial No. 08/808,827 provides several safety benefits. First, since the regulatory elements normally found within the 3' U3 sequences of the retroviral vector are removed, the therapeutic gene is not expressed except in those tissues in which the heterologous promoter and/or regulatory elements are active. Thus, particularly in those embodiments where the coding sequences encode a suicide gene, incorporation of the retroviral vector into non-target cells should not result in adverse side effects because the coding sequences are not expressed. Second, the use of heterologous promoters and/or regulatory elements reduces the likelihood that recombination between the vector and sequences present within either the cell lines used to create the vector or endogenous sequences in the host will result in the production of replication competent vectors. This is particularly important for the therapeutic use of

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retroviral vectors, because while it is believed that most researchers assume that the probability of a replication defective vector integrating into the genome of the target cell and insertionally activating an oncogene near the insertion site is small, if a replication competent retrovirus were produced, the expansion of the population of replication competent viruses would be expected to increase this probability exponentially. Given that the instantly claimed retroviral vectors comprise partially or completely deleted 3' U3 regions and employ heterologous promoters therein, the probability of generating a replication competent virus from the instantly claimed retroviral vectors is believed to be much lower than when using the Couture vectors, which employ complete 3' LTRs that have 3' U3 sequences that are highly homologous to wild-type retroviruses.

11. The deletion of 3' U3 sequences and insertion of heterologous promoters into the 3' U3 is not suggested by the combination of Couture and Faustinella as contended by the United States Patent and Trademark Office. While Couture appears to suggest that replacement of 3' U3 sequences with the corresponding sequences from related retroviruses to restore a complete 3' U3 region might result in expression of coding sequences present within the body of the vector, Couture also states a correlation between expression levels and the degree of homology between the sequences that were exchanged. According to Figure 2 of Couture, the homology between the Mo-MuLV U3 that was removed and the U3 regions that were inserted was 99% for HaMSV, 98% for MPSV, 76% for AKV, 74% for SL3-3, and 64% for Xeno. Table 3 of Couture indicates that the ability of the chimeric LTRs to direct expression of the coding sequence correlated with the degree of homology to Mo-MuLV in each cell line tested. Thus, Couture strongly suggests that as the degree of homology between the Mo-MuLV U3 region that is removed and the promoter that is inserted decreases, the ability of the promoter to regulate expression of a gene present within the body of the vector also decreases. Given that these vectors are contemplated for therapeutic use in subjects, the expression level that can be generated by the recombinant vector is of importance. Thus, no scientific basis is believed to be found in Couture and Faustinella to motivate the use of a polylinker to construct the vectors, as disclosed by Faustinella, since the

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since the presence of a polylinker would reduce the homology levels in reconstructing the complete 3' U3 region as disclosed by Couture, which would be expected to reduce expression levels based on the above-mentioned observation in Couture.

12. It is also believed that Couture teaches against the use of cellular promoters because the sequences of such promoters would be expected to have even less homology to Mo-MuLV than did the Xeno sequences disclosed in Couture, and thus would be expected to result in low and likely unsatisfactory expression levels. Thus, no scientific basis is believed to be found in Couture and/or in Faustinella to motivate the use of promoter and/or regulatory sequences from cellular genes, and correspondingly, the use of a polylinker to construct the vectors. Thus, it is believed that there would be no motivation to look to Faustinella having considered the teachings of Couture to construct a retroviral vector.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Christine Leib-Moesch

14 April 2005

Date

Attachment: Exhibit A

Exhibit A

CURRICULUM VITAE

Christine Leib-Mösch

Personal data:
Date of birth: March 11, 1950
Nationality: German

Education:

1969 - 1975	Technical University, Munich, Diploma in Chemistry
1975 - 1979	Graduate student, Ludwig-Maximilians-University of Munich
1979	PhD, Biochemistry
1993	Habilitation, venia legendi for Experimental Oncology, University of Heidelberg

Previous positions:

1979 - 1980	Postdoctoral fellow at the Institute of Biochemistry, Univ. of Munich
1980 - 1989	Research scientist, Medical Policlinic, University of Munich
1989 - 1993	Research scientist, Medical Clinic III Mannheim, University of Heidelberg
1994 - 2000	Associate professor (C2), Medical Clinic III Mannheim, University of Heidelberg
1980 - 2000	Guest scientist, Institute of Molecular Virology, GSF-Research Center for Environment and Health, Neuherberg

Current positions:
Leader of research group "Human Endogenous Retroviruses" at the Institute of Molecular Virology, GSF-Research Center for Environment and Health, Neuherberg and Medical Clinic III Mannheim, University of Heidelberg,
Appointment as apl. Professor, University of Heidelberg (2000)

Fields of Interest:
Retroviruses and retroviral vectors, retroviral gene expression, retroviruses in carcinogenesis and autoimmune diseases, role of retroelements in evolution, prion diseases

X. Related Proceedings Appendix

None.